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REVIEW

Cell fate regulation governed by p53: Friends or reversible foes in cancer therapy

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Abstract

Cancer is a leading cause of death worldwide. Targeted therapies aimed at key oncogenic driver mutations in combination with chemotherapy and radiotherapy as well as immunotherapy have benefited cancer patients considerably. Tumor protein p53 (*TP53*), a crucial tumor suppressor gene encoding p53, regulates numerous downstream genes and cellular phenotypes in response to various stressors. The affected genes are involved in diverse processes, including cell cycle arrest, DNA repair, cellular senescence, metabolic homeostasis, apoptosis, and autophagy. However, accumulating recent studies have continued to reveal novel and unexpected functions of p53 in governing the fate of tumors, for example, functions in ferroptosis, immunity, the tumor microenvironment and microbiome metabolism. Among the possibilities, the evolutionary plasticity of p53 is the most controversial, partially due to the dizzying array of biological functions that have been attributed to different regulatory mechanisms of p53 signaling. Nearly 40 years after its discovery, this key tumor suppressor remains somewhat enigmatic. The intricate and diverse functions of p53 in regulating cell fate during cancer treatment are only the tip of the iceberg with respect to its equally complicated structural biology, which has been painstakingly revealed. Additionally, *TP53* mutation is one of the most significant genetic alterations in cancer, contributing to rapid cancer cell growth and tumor progression. Here, we summarized recent advances that implicate altered p53 in modulating the response to various cancer therapies, including chemotherapy, radiotherapy, and immunotherapy. Furthermore, we also discussed potential strategies for targeting p53 as a therapeutic option for cancer.

KEYWORDS
cancer, chemotherapy, drug targeting, immunotherapy, p53, tumor suppressor

List of abbreviations: 5-FU, 5-fluorouracil; ABCB1, adenosine triphosphate-binding cassette subfamily B member 1; ABCG2, adenosine triphosphate (ATP)-binding cassette efflux transporter G2; ACT, adoptive cell transfer; ALDH, aldehyde dehydrogenase; ALDH1A1, aldehyde dehydrogenase 1A1; ALS, amyotrophic lateral sclerosis; AML, acute myeloid leukemia; AML, acute myeloid leukemia; APC, antigen-presenting cell; APL, acute promyelocytic leukemia; ARF-BP1, ADP-ribosylation factor-binding protein 1; ASPP, apoptosis stimulating

1 | BACKGROUND

Cancer is a group of diseases characterized by abnormal and uncontrolled cellular growth, primarily caused by genetic mutations [1, 2]. These mutations, known as "drivers", have the ability to initiate tumor formation and provide selective advantages to cells in comparison to neighboring cells [3]. The genes that harbor these driver mutations are referred to as "cancer driver genes". The mutant proteins encoded by these genes affect various essential cellular functions. Furthermore, the discovery of these driver mutations has led to the development of targeted anticancer therapy and the search for genomic biomarkers to predict prognosis and therapeutic responses in cancer.

protein of p53; ATG12, autophagy related 12; ATM, ataxia-telangiectasia mutated; ATO, arsenic trioxide; ATR, ATM- and Rad3-related kinase; AURKA, aurora kinase A; BAK, bcl2 antagonist/killer 1; BCL, B cell lymphoma/leukemia; BECN1, beclin 1; BRCA1, breast cancer 1 protein; BubR1, budding uninhibited by benzimidazole 1-related 1; CAF, cancer-associated fibroblast; CAR-T, chimeric antigen receptor T; CBP, CREB-binding protein; CC, chemotactic cytokine; CCLE, cancer cell line encyclopedia; CDDP, cisplatin; CDK, cyclin-dependent kinase; CDKN1A, cyclin-dependent kinase inhibitor 1A; CDX, cell-derived xenograft; CDX, cell line derived xenograft; CHIP, Hsc70-interacting protein; CHK1/2, checkpoint kinase 1/2; CIRT, carbon ion radiotherapy; CK2, casein kinase II; COP1, constitutive photomorphogenic 1; COVID-19, coronavirus disease 2019; CRD, C-terminal regulatory domain; CRM1, chromosomal region maintenance 1; CSC, cancer stem cell; CTD, C-terminal domain; CTM, chetomin; CXC, C-X-C Motif Chemokine Receptor 4; CYP3A4, CYP450 enzyme 3A4; CYP450, cytochrome P450; DAB2IP, disabled homolog 2 interacting protein; DBD, DNA-binding domain; DC, dendritic cells; dCK, deoxycytidine kinase; DDR, DNA damage response; DNE, dominant negative effect; DRAM1, damage-regulated autophagy modulator 1; DSB, DNA double-strand break; DYRK2, dual specificity tyrosine phosphorylation regulated kinase 2; E2F1, E2 promoter binding factor 1; EBRT, external beam radiation therapy; ECM, extracellular matrix; EFNB2, ephrin-B2; EGFR, epidermal growth factor receptor; EMA, European Drug Administration; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; ESC, embryonic stem cell; ESCC, esophageal squamous cell carcinoma; ETS1, E26 oncogene homolog 1; ETS2, E26 transformation-specific proto-oncogene 2; FBXW7, f-box and WD repeat domain containing 7; GADD45, growth Arrest and DNA Damage-inducible 45; GB, glioblastoma; GEMM, genetically engineered murine model; GI, gastrointestinal; GLS2, glutamine synthase 2; GLUT1, glucose transporter 1; GOF, gain of function; H. pylori, Heliobacter pylori; HAT, histone acetyltransferase; HDAC6, histone deacetylase 6; HIF, hypoxia-inducible factor; HIPK2, homeodomain-interacting protein kinase 2; HLA, human leukocyte antigen; hMMP-13, human matrix metalloproteinase-13; HPV, human papillomavirus; HSP, heat shock protein; IAA, isoamylamine; IARC, International Agency for Research on Cancer; ICD, immunogenic cell death; ID4, Inhibitor of DNA-binding 4; IFN, Interferon; IFN-β, interferon-β; iIL-1, interleukin 1; IL, Interleukin; iPSC, induced pluripotent stem cell; iPSC, induced pluripotent stem cells; IR, Ionizing radiation; IRF, IFN regulatory factor; KAT, lysine acetyltransferase; KMT, lysine methyl transferase; KO, knockout; KO, knockout; LC, Local tumor control; LDH, lactate dehydrogenase; Lgr5, leucine-rich-repeat-containing G-protein-coupled receptor 5; LRPPRC, leucine-rich pentatricopeptide repeat-containing protein; LSD1, lysine-specific demethylase 1; LSD1, lysine-specific demethylase 1; MAFF, musculoaponeurotic fibrosarcoma oncogene homolog F; MCM4, minichromosome maintenance 4; MCT, monocarboxylate transporter; MDM2, murine double minute 2; MDR, multidrug resistance; MDR1, multidrug resistance gene 1; MDS, myelodysplastic syndromes; MDSC, myeloid-derived suppressor cell; MEF, mouse embryonic fibroblast; MET, mesenchymal-epithelial transition factor; MHC, major histocompatibility complex; MLL1, mixed lineage leukemia 1; MLL2, mixed lineage leukemia 2; MMPs, Matrix metalloproteinases; MOF, males absent on the first; MOZ, monocytic leukemia zinc finger protein; MRN, Mre11-Rad50-NBS1; mTOR, mammalian target of rapamycin; Mut-p53, mutant p53; MVA, modified vaccinia Ankara; MVAp53, modified vaccinia Ankara vaccine encoding WT p53; NES, nuclear export signal; NF-Y, nuclear factor Y; NF-κB, nuclear factor-κB; NHE, Na^+/H^+ exchanger; NK, natural killer; NK, natural killer; NSCLC, non-small cell lung cancer; OD, oligomerization domain; p53BP1, p53 binding protein 1; PAH, polycyclic aromatic hydrocarbons; PARP1, poly (ADP-ribose) polymerase-1; PCNA, proliferating cell nuclear antigen; PD-1, programmed cell death protein 1; PDGFRb, PDGF receptor b; PD-L1, programmed death-ligand 1; PDX, patient-derived xenograft; PDX, patient derived xenograft; PGC-1a, Peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PIAS, protein inhibitor of activated stat; PKC, protein kinase C; PKM2, pyruvate kinase M2; PLK1, polo-like kinase 1; PLK4, polo-like kinase 4; PML, promyelocytic leukemia protein; PML-RARα, promyelocytic leukemia-retinoic acid receptor α; PPMID, phosphatase protein phosphatase magnesium-dependent 1; PRD, proline-rich domain; PRMT5, protein arginine N-methyl transferase 5; PSA, prostate-specific antigen; PTMs, posttranslational modifications; PTX, paclitaxel; RB1, retinoblastoma protein 1; RCP, Rab-coupling protein; ROCK, Rho-associated coiled-coil kinase; RRM2b, ribonucleotide reductase small subunit B; RT, radiotherapy; SCLC, small cell lung cancer; SCO2, synthesis of cytochrome C oxidase 2; SDF-1, stromal cell-derived factor-1; SEN1/2, single dominant gene 1/2; siRNA, small interfering RNA; SLMP53-2, (S)-tryptophanol-derived oxazoloisoindolinone 2; SMYD2, SET and MYND domain-containing protein 2; snoRNA, small nucleolar RNA; SNP, single-nucleotide polymorphism; SOCS1, suppressor of cytokine signaling 1; SOD1, superoxide dismutase 1; SREBP, sterol regulatory element binding proteins; STAT1, signal transducer and activator of transcription 1; STAT3, signal transducer and activator of transcription 3; SUMO, small ubiquitin-like modifier; SWI/SNF, switch/sucrose non-fermentable; T3SS, type III secretion system; TAD, N-terminal transactivation domain; TAM, tumor-associated macrophage; TCGA, The Cancer Genome Atlas; TCR, T cell receptor; TCR-m, T cell receptor mimic; TD, tetramerization domain; TDP-43, transactive response DNA binding protein of 43 kDa; TF, transcription factor; TIGAR, TP53-induced glycolysis and apoptosis regulator; TIL, tumor-infiltrating lymphocytes; TIME, tumor immune microenvironment; TK1, thymidine kinase 1; TLR, Toll-like receptor; TME, tumor microenvironment; Topors, TOP1 binding arginine/serine-rich protein; TRIM69, tripartite motif 69; TSC2, tuberous sclerosis complex subunit 2; ULBP1, UL16-binding protein 1; UMD, Universal Mutation Database; UREB1, UBA And WWE Domain Containing E3 Ubiquitin Protein Ligase 1; US FDA, United States Food and Drug Administration; USF1, upstream transcription factor 1; VDAC, voltage-dependent anion-selective channel; VEGF, vascular endothelial growth factor; WIP, WASP interacting protein; WT, wild-type; WT, wild-type; YAP, yes-associated protein; YAP1, Yes-associated protein 1; ZEB-1, zinc-finger E-box binding homeobox 1.

The tumor suppressor p53 acts as a major barrier against cancer initiation and progression. Biochemically, p53 functions primarily as a sequence-specific transcription factor (TF) capable of binding to defined DNA sequences within the genome (called p53 response elements or p53-binding sites) and activating the transcription of adjacent genes as well as more distant genes that are regulated by enhancers with p53-binding sites [4]. In addition, p53 can repress the transcription of a large subset of genes, usually by indirect mechanisms [5]. Notably, p53 is regulated by many critical endogenous protein factors, including murine double minute 2 (MDM2)/human double minute 2 (HDM2), p53-induced RING-H2 (Pirh2), Dicer, ADP-ribosylation factor-binding protein 1 (ARF-BP1), silent information regulator sirtuin 1 (SIRT1), CREB-binding protein (CBP)/E1A-binding protein (p300) and JNK, via posttranslational modifications such as ubiquitination and phosphorylation [5–7]. The activity of the E3 ubiquitin ligase MDM2, one of the most common negative regulatory factors of p53, causes p53 to be extremely unstable, with a half-life of only 6-40 minutes, maintaining low p53 protein levels in normal unstressed cells through constitutive proteasomal degradation [8]. In contrast, the loss of p53-induced apoptosis and cell cycle arrest in cancer cells resulting from MDM2 upregulation by gene amplification may result in chemotherapy and radiotherapy (RT) failure and a poor prognosis [9]. Additionally, Pirh2 possesses ubiquitin-protein ligase activity, which can induce MDM2-independent p53 ubiquitination and degradation to inhibit its transactivation activity [10].

Mutations in the tumor protein p53 (*TP53*) gene, which abrogate the tumor suppressor activities of its encoded protein p53, are the most common single gene alterations in human cancers and are recognized as driving events in various types of tumors [11–13]. Consequently, attempting to restore the functionality of p53 in tumors has become a therapeutic strategy. The ability of such restoration to trigger cancer cell death was first documented decades ago [14]. However, most of these efforts have had limited success: very few small-molecule drug development initiatives have reached late-stage clinical trials, and none have been approved by the European Drug Administration (EMA) or the United States Food and Drug Administration (US FDA) [14]. These failures are probably partially because p53, as a nuclear TF, does not possess typical drug target features and has therefore long been considered undruggable and because the main consequence of *TP53* mutations is loss of its tumor suppressor function as well as endowment of gain of functions (GOFs) that contributes to malignant cancer progression [15]. However, several promising approaches toward p53-based cancer therapy, including chemotherapy, RT and immunotherapy, have recently emerged. In addition, gene therapy strategies that fall under the broad category of cancer immunotherapy are also experiencing a revival, with the expectation that such "personalized" drugs will have fewer undesirable side effects. This revival is due to the emergence of novel approaches that may make targets druggable through the incorporation of new insight into p53's new functions and the improved understanding of the mechanisms of action and modes of drug delivery [5].

Given its role in multiple diverse pathways and biological outcomes [16], p53 is appropriately subject to tight regulation [17], because too little p53 activity or an aberrant p53 status (such as p53 mutation) can result in tumor development [18], whereas too much p53 activity or an aberrant p53 status induces indiscriminate cell cycle arrest [19] and cell death [20, 21]. For example, both experimental and clinical studies have shown that the activation of endogenous wild type (WT) p53 is vital to RT- and chemotherapy-induced cytotoxicity, while p53 inactivation has been associated with resistance or insensitivity to treatment [22, 23]. In addition, cancer immunotherapy regimens have recently generated great enthusiasm owing to their unprecedented success in several types of cancer. This review highlighted recent progress in understanding how p53 differentially regulates cell fate in response to different stress stimuli during cancer treatment. It explored the different ways in which p53 alterations can promote cell survival. It highlights the recent understanding of p53's interaction with regulators of cellular communication, such as the tumor microenvironment (TME) and microbiome. We also discuss the potential of combining p53-based treatment with newly developed cancer therapies like chemotherapy, radiotherapy and immunotherapy to improve cancer treatments. Furthermore, it provides insights into the current state of the development of p53 pathway modulators and the challenges faced during preclinical and clinical development of new small-molecule drug targets.

2 | ORIGIN, HISTORY, AND PROGRESSION OF THE P53 SIGNALING PATHWAY

In 1979, over 40 years ago, p53 was first discovered in complex with the SV40 large T antigen in virally transformed cells [24, 25]. *TP53* was initially classified as an oncogene, possibly because initial studies inadvertently used a mutated p53 cDNA. However, in 1989, further studies showed that p53 inhibited the growth of cultured cells and oncogenic transformation, and it was thus reclassified as a tumor suppressor [26, 27]. Subsequently, numerous relevant studies have confirmed that p53 is not an oncogene, although mutation of the *TP53* tumor suppressor

gene is the most common genetic alteration in cancers. Almost 1,000 alleles have been identified in various human tumors [28]. While virtually all p53 mutations are thought to compromise WT p53 activity, the prevalence and recurrence of missense *TP53* alleles has prompted countless studies aimed at understanding the function of the resulting mutant (mut)-p53 proteins. In addition, in vivo studies of p53-null mice have corroborated the in vitro data: while p53-null mice were developmentally normal, they ultimately developed tumors with nearly 100% penetrance [19]. Over the past two decades, studies have gradually revealed the structure, function and role of p53 in tumorigenesis and tumor development [17, 29, 30]. Along with the first successful elucidation of the crystal structure of the p53-DNA complex in 1994 [31], the function of p53 was gradually revealed: p53 functions as a TF induced by various stimuli that in turn induces cell cycle arrest, apoptosis and senescence [21]. These distinct stress responses are regulated by subsets of p53 target molecules, including p21, p53 up-regulated modulator of apoptosis (Puma), Tiger and plasminogen activator inhibitor 1 (PAI-1), which respond to different p53-activating conditions [32]. Mechanistically, p53 is a versatile stress-responsive TF that functions alone or in cooperation with other factors. Upon activation, p53 tetramers bind in a sequence-specific manner to DNA response elements consisting of two decametric half-site motifs with the general form RRRCWWGYYY (R = A, G; W = A, T; Y = C, T) separated by 0-13 base pairs [33]. After binding to DNA, p53 activates a range of biological cellular events, as well as the E3 ligase MDM2, to create a negative feedback loop that ultimately leads to its degradation [16, 17, 21, 32, 34–36]. Although the majority of mutations occur in the DNA-binding domain (DBD) and many structural mutations affect p53's DNA-binding capacity, there are mutants that are known to bind to DNA. It seems to largely explain the role of p53 in tumor formation [37].

In addition, new insights into the occurrence of hotspot mutations and the resulting biological consequences in tumor development are offered by the following three main differences [12]. Some studies support three distinct but perhaps not necessarily mutually exclusive mechanisms by which different p53 mutants impact cancer: first, they lose the ability to execute WT p53 functions to varying degrees; second, they act as dominant negative inhibitors of WT p53-mediated tumor-suppressive programs; and third, they may gain oncogenic functions that go beyond mere p53 inactivation [38, 39]. Among the possibilities, the GOF hypothesis is the most controversial, partially due to the dizzying array of biological functions that have been attributed to different mut-p53 proteins [12]. Owing to disruption of the p53-MDM2 negative feedback loop, many p53 mutants are stabilized, allowing them to engage in aberrant interactions with other cellular factors, potentially altering their functions and leading to GOF phenotypes [12, 40–42]. However, the potential GOF effects of p53 mutants have been a topic of debate for nearly 30 years. The p53 protein mutations that may result in the largest GOF effect was first discovered by Levine and colleagues, who showed that ectopic expression of certain TP53 mutant alleles can activate the expression of multidrug resistance (MDR) reporter genes [43], whereas WT alleles cannot [7, 44–47]. Later, two other groups found that although mice engineered to harbor germline missense mutations (R175H and R273H) succumbed to cancer at a rate similar to that of p53-null mice, they exhibited a broader tumor spectrum and a higher incidence of metastasis [48, 49]. These data were considered decisive evidence of a GOF effect.

Considering the unassailable position of *TP53* among cancer "driver" genes, one would expect that this tumor suppressor would be the most sought-after target for anticancer therapies. However, the relevance of p53 to clinical oncology has lagged behind its reputation as a key player in tumorigenesis. Major milestones in research efforts to therapeutically target mut-p53 include the initial demonstration of its dominant negative and GOF effects, which provided important insights into the mechanistic basis underlying the tumorigenic capacity of mut-p53 [50–55]. Collectively, the identification of temperature-sensitive mutations and secondary site suppressor mutations, which indicated that mut-p53 can be refolded into a WT conformation and thus function as a tumor suppressor [56, 57], along with the evidence indicating that antibodies against the C-terminus of WT p53 promote its DNA-binding activity (and might have the same effect on p53 variants) and that peptides derived from the p53 C-terminal domain (CTD) can restore wild-type function to mut-p53 [58–60], form the basis for the development of small molecules that could target mut-p53 [58]. Experimental therapeutic strategies predicated on the p53 status were, however, initially focused on targeting cells without functional p53 [61]. For example, early approaches relied on the synthetic lethal interaction between loss of p53 function and inhibition of protein kinase C (PKC), with the use of the oncolytic virus ONYX-15 to selectively kill cancer cells with inactive p53 [62, 63]. Moreover, attempts have been made and are ongoing in China to directly reintroduce WT p53 into cancer cells via gene therapy approaches, despite a multitude of challenges, including the possibility that reconstituted WT p53 is subject to the dominant negative effect (DNE) of endogenous mut-p53 [29].

In parallel to the abovementioned efforts, reactivation of the p53 pathway in cancers with *TP53* mutations (accounting for ~50% of all human cancers) has been the focus of intense research. In addition, pharmacologically superior

"stable peptides", small synthetic proteins that are locked into their bioactive conformation through the site-specific introduction of a hydrocarbon brace (chemical staple), can rescue WT p53 by inhibiting its interaction with MDM2 and MDM4 and are being developed for this purpose [64, 65]. These molecules will probably benefit patients with tumors harboring WT p53, provided that their pharmacological properties can be optimized to diminish the occurrence of adverse effects. However, such treatments are expected to be detrimental in patients with tumors harboring mut-p53, because the resulting elevated level of mut-p53 is expected to exacerbate the DNE or GOF effects to promote tumor growth and therapeutic resistance [66]. Hence, caution is required when considering the use of these targeted p53 reactivators.

In particular, the restoration of WT functions in cells with mut-p53 has been pursued vigorously. Multiple agents with this ability have been identified, with CP-31398 being the first to be demonstrated in 1999 [64]. Since then, only two such drugs, namely, PRIMA-1^{met} and arsenic trioxide (ATO, also known as Trisenox), have reached clinical trials. The small molecule PRIMA-1^{met} has been discovered to bind to thiol groups located in the core domain of mut-p53 and stabilize the WT conformation [67]. PRIMA-1^{met} is currently being evaluated in phase III clinical trials and was approved by the US FDA in 2019 for the treatment of myeloid syndrome. ATO is an US FDA-approved drug to treat acute promyelocytic leukemia (APL) that is characterized by the expression of promyelocytic leukemia-retinoic acid receptor α (PML-RARα) fusion protein [68, 69]. In 2021, Chen *et al.* [70] demonstrated that ATO rescued p53 activity from structural mut-p53 through promotion of p53 folding by covalently binding to multiple cysteines in p53. Currently, several clinical trials to examine the effects of ATO on inhibiting p53-mutated cancers myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), refractory solid tumors, recurrent and metastatic ovarian and endometrial cancer) are underway (NCT03855371, NCT04869475, NCT04489706, and NCT04695223) [71]. However, the outcomes of these studies have not yet been reported. Zinc is crucial for the correct folding and function of p53. Metal chaperones play a role in increasing the concentration of intracellular zinc ion, which facilitates the binding of zinc ions to mut-p53 [72]. This binding leads to a conformational shift towards the WT structure. These compounds appear to restore WT p53 activity on mut-p53 to varying degrees, but fall far short of the expected results of converting all mut-p53 molecules to a fully "WT-like" state [12, 14]. Another molecular therapeutic strategy is based on the function of molecular chaperones that can drive the correct folding and stabilization of misfolded or improperly folded proteins, which in turn can be expressed to perform their functions. To date, researchers have identified two compounds based on this effect, namely, chetomin (CTM) and (S)-tryptophanol-derived oxazoloisoindolinone 2 (SLMP53-2), which can indirectly induce a conformational shift of p53 to the WT conformation by interacting with heat shock protein (Hsp40) and Hsp70, respectively, and then exert antitumor effects, as shown in vivo [14, 18]; however, these compounds remain in the experimental stage and have not entered clinical trials.

While the tumor suppressor functions of p53 have long been recognized, the contribution of p53 to numerous other aspects of disease and physiology is only now being appreciated [34]. In the last decade, new regulatory functions of p53 have been revealed, including its participation in tumor cell energy metabolism [73], microbial metabolism [74, 75] and ferroptosis [76], normal cell repair processes, and whole-genome evolution [77]. However, there are still many challenges as well as perspectives in future research, which will hopefully be addressed, mainly through the following points. (1) What are the biophysical, biochemical, and atomic details underlying the actions of p53 alone and in complex with MDM2/MDMX? (2) Is p53 clinically druggable? (3) Can p53 activity be analyzed by imaging in cells, tissues, and even animals? (4) Is p53 a metabolic regulator, a guardian of the genome, or both in all cells and tissues? (5) What levels of p53 expression are enough and too high? (6) Can artificial intelligence (AI) be used to model the biological function of p53 in cells or in vivo? (7) Do p53 molecules in different cells or tissues physiologically communicate with one another in vivo, and if so, how? In addition, as the key molecule in cancer therapy that is mutated more frequently than any other protein, p53 is called the "proverbial holy grail" for targeted drugs. Although dozens of p53-targeting compounds have been reported in recent decades, the scientific challenges of restoring p53 function and targeting p53, which has no pocket and no logical targeting strategy, have remained unmet. Therefore, based on whether the continuous development of these research techniques and methods can overcome this bottleneck, there will be a groundbreaking era for p53 research that will usher in a revolutionary breakthrough. With the emergence of modern biotechnologies and AI, this limitation is expected to be overcome in the future (Figure 1).

3 | VARIOUS MODELS OF P53 REGULATION IN RESPONSE TO DIFFERENT STRESS SIGNALS

Originally, p53 was called "the guardian angel of the genome", because it was found to be activated in response to various types of genotoxic stress, including DNA

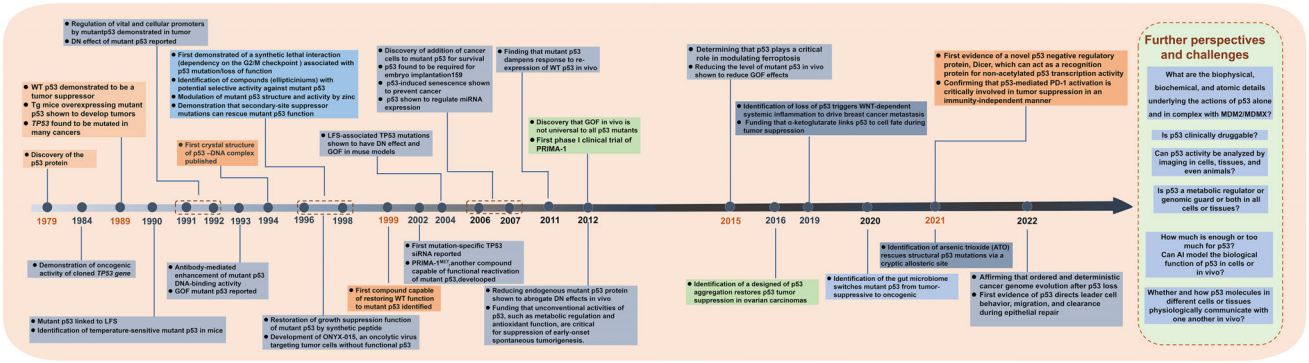

FIGURE 1 History of the p53 signaling pathway and the road to targeting p53, with remaining challenges. This timeline shows the major breakthroughs that have fueled ongoing efforts to target mut-p53 for anticancer therapy. Further perspectives: the future of p53 research. Several remaining challenges: (1) What are the biophysical, biochemical, and atomic details underlying the actions of p53 alone and in complex with MDM2/MDMX? (2) Is p53 clinically druggable? (3) Can p53 activity be analyzed by imaging in cells, tissues, and even animals? (4) Is p53 a metabolic regulator, a guardian of the genome, or both in all cells and tissues? (5) What levels of p53 expression are enough and too high? (6) Can Al be used to model these features in cells or in vivo? (7) Do p53 molecules in different cells or tissues physiologically communicate with one another in vivo, and if so, how? Data were retrieved from and based on [7, 12, 14, 605]. WT, wild type; LFS, Li-Fraumeni syndrome; DN, dominant negative; GOF, gain of function; AI, Artificial Intelligence; TP53, tumor protein p53;miRNA, microRNAs; siRNA, small interfering RNA

damage [78]. Later research showed that p53 functions as a central hub to manage a broad range of cellular stresses, both endogenous and exogenous [79]. These stresses include oncogene activation, telomere erosion, ribosomal stress, and hypoxia [7, 21, 80]. such as oncogene activation, telomere erosion, ribosomal stress, and hypoxia. Once activated, it can regulate many cellular processes, such as cell cycle arrest, DNA repair, apoptosis, ferroptosis, immunity, senescence, autophagy, and pyroptosis or necroptosis, to promote cell survival or limit the malignant transformation of cells. In addition to its role in cancer suppression, p53 also participates in the modulation of cell metabolism (Figure 2). Moreover, accumulating data indicate transcription-independent roles of p53. The functions of p53 range far beyond managing DNA damage [7, 16]. Considering these observations, p53 should be regarded not as a simple "guardian of the genome" but as an all-powerful "guardian of the cell" [16].

3.1 | Roles of p53 posttranslational modifications in tumorigenesis

Since p53 plays many vital roles in cell fate, its functional regulation is of crucial importance. There are many layers of mechanisms that modulate p53 expression and function. For example, p53 can be regulated at the genetic level, by alterations such as mutation [81] or single-nucleotide polymorphisms (SNPs) [82]; at the post-transcriptional level, by mechanisms such as epigenetic inhibition of p53 transcription [83]; at the transcriptional level, by mechanisms such as alternative splicing [84]; and at the protein level, by processes such as protein folding [85] and localization [86]. p53 contains many conserved sites that can contribute to p53 regulation by undergoing a multitude of covalent posttranslational modifications following genotoxic stress, including phosphorylation, modification with ubiquitin and other ubiquitin-like proteins, acetylation, methylation, glycosylation, SUMOylation, hydroxylation, O-GlcNAcylation, ADP-ribosylation and peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1)-mediated prolyl isomerization [87], leading to enhanced protein stability and nuclear translocation [87, 88].

Moreover, p53 contains an array of amino acids subject to various kinds of posttranslational modifications [88], which are concentrated mainly in the tetramerization domain (TD) and CTD. The earliest discovered characteristic of individual modifications of p53 is the redundancy of many amino (N)-terminal and carboxyl (COOH, C)-terminal modifications, which is characterized by either the flexible correspondence between the enzymes and the modifications or the subtle effects exerted by mutation of a single site [89, 90]. This can be explained by either the complementarity among the modifications or the additive or synergistic performance of the modifications. Both mechanisms indicate the importance of the crosstalk among the modifications. To date, more than 222 different post-translational modifications (PTMs) on 99 residues of endogenous p53 have been detected by mass spectrometry analysis [91]. These modification types have some common features. (1) Multiple sites: each modification type can occur on many different amino acids, and some amino acids can be modified by different chemical groups. (2) Multiple functions: the functions of the

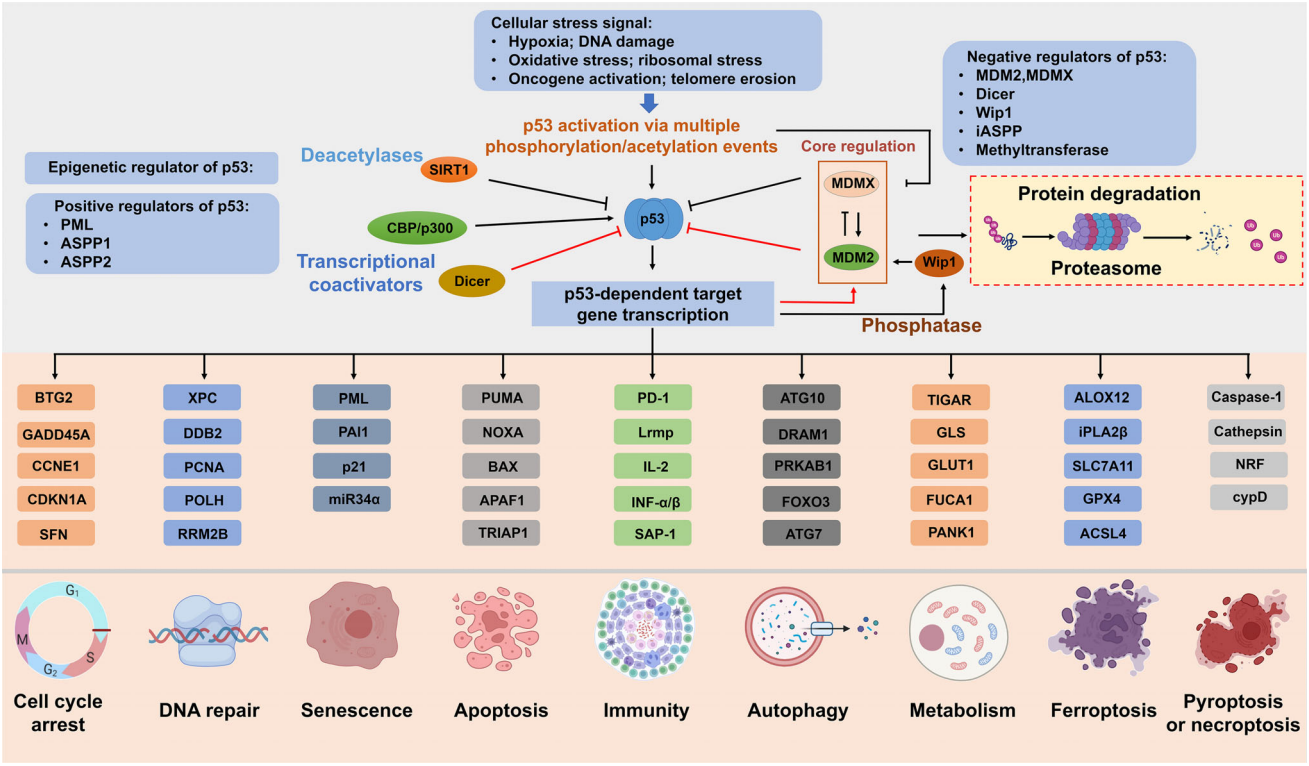

FIGURE 2 The multiple functions of p53 regulators in response to cellular stress signals. In response to a specific stress or a combination of stresses, p53 signaling can be activated in cells. Proteins activated by stress signals then activate p53-mediated transcription of genes whose protein products are involved in a range of downstream cellular processes, as well as genes involved in positively or negatively regulating p53 and/or p53-dependent transcription, resulting in downstream responses as well as the generation of feedback loops. The p53 transcriptional network contains target genes that regulate diverse cellular processes, including apoptosis, cell cycle arrest (including senescence), autophagy, DNA repair, metabolism, immunity, and cell death (ferroptosis, pyroptosis and necroptosis). Data were retrieved from and based on [16, 18, 201]. PML, promyelocytic leukemia;ASPP1, apoptosis stimulating of p53 protein 1; PUMA, p53 upregulated modulator of apoptosis; ASPP2, apoptosis stimulating of p53 protein apoptosis stimulating of p53 protein 2; SIRT1, silent information regulator sirtuin 1; CBP, CREB-binding protein; iASSP, Inhibitory Member of the ASPP (Apoptosis-stimulating protein of p53); Wip1, wild-type p53-induced phosphatase-1; MDM2, Mouse double minute 2; MDMX, Mouse double-minute 4; CDKN1A, cyclin-dependent kinase inhibitor 1A; IL-2, Interleukin-2; BTG2, B-cell translocation gene 2; GADD45A, growth arrest and DNA damage protein 45A; CCNE1, cyclin E1; SFN, stratifin; XPC, xeroderma pigmentosum group C; DDB2, damage-specific DNA-binding protein 2; PCNA, proliferating cell nuclear antigen; POLH, DNA polymerase Eta; RRM2B, ribonucleotide reductase regulatory TP53 inducible subunit M2B; PAI1, plasminogen activator inhibitor 1; miR34α, microRNA 34 alpha; NOXA, phorbol-12-myristate-13-acetate; BAX, bcl-2-associated X protein; APAF1, apoptotic protease-activating factor 1; TRIAP1, TP53-regulated inhibitor of apoptosis 1; PD-1, programmed cell death 1; INF-α/β, interferon alpha/beta; SAP-1, saposin-like protien-1; ATG10, autophagy-related 10; DRAM1, damage-regulated autophagy modulator 1; PRKAB1, protein kinase AMP-activated non-catalytic subunit beta 1; FOXO3, forkhead box O3; TIGAR, TP53-induced glycolysis and apoptosis regulator; GLS, glutaminase; FUCA1, α-l-fucosidase 1; PANK1, pantothenate kinase 1; ALOX12, arachidonate 12-lipoxygenase; IPLA2β, independent phospholipase A2β; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; ACSL4, Acyl-CoA synthetase long-chain family member 4; NRF, nuclear respiratory factor

modifications are site-, type- and context-dependent, and the same modification may have disparate effects at different sites; however, different modifications can exert similar effects. (3) Reversibility: for each modification, there is also at least one corresponding enzyme that removes the modification. (4) Widespread crosstalk: modifications can influence the effects of modifications at other sites. The basic action mechanisms of these modifications include affecting p53 stability and localization, causing protein conformational changes, providing interacting partner docking motifs, and altering local electrostatic forces [92]. These features and modes are reiterated in Figure 3.

3.1.1 | Phosphorylation of p53 is a critical modification guiding its regulation of apoptotic cell fate

Among the abovementioned modifications, modifications on specific residues, particularly phosphorylation and acetylation, contribute to the ability of p53 to differentially

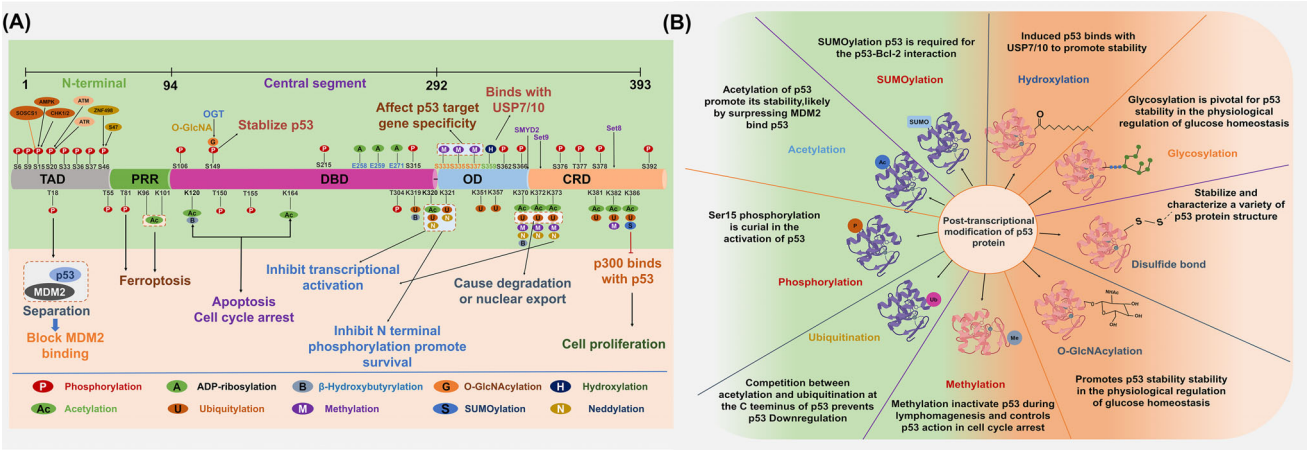

FIGURE 3 Overview of PTMs at various sites of p53 and their regulatory functions. (A) The major sites of p53 modifications (phosphorylation, ubiquitination, SUMOylation, neddylation, acetylation, methylation, O-GlcNAcylation, ADP-ribosylation, hydroxylation, and β-hydroxybutyrylation) are plotted. (B) Different colors are used to differentiate distinct modification types. Representative functions of some modifications are indicated. Data were retrieved from and based on [88, 90, 122]. TAD, transactivation domain; PRR, proline-rich region; DBD, DNA-binding domain; OD, oligomerization domain; CRD, C-terminal regulatory domain; USP7/10, ubiquitin-specific protease 7/10; OGT, O-linked N-acetylglucosamine transferase

activate cell cycle arrest or apoptosis genes [93]. For example, p53 contains an array of serine (S)/threonine (T) phosphorylation sites that span the entire protein but are concentrated in the N-terminal transactivation domain (TAD) and the C-terminal regulatory domain (CRD) [90] (Figure 3A). As early as 1992, Hupp *et al.* [58] reported that casein kinase II (CK2) can phosphorylate p53 at a C-terminal site to promote its DNA binding. In addition, p53 is usually phosphorylated at S15, which is located in 2 TADs of the p53 structure. Several kinases, including ataxia-telangiectasia mutated (ATM) kinase, ATM- and Rad3-related (ATR) kinase, and checkpoint kinase 1/2 (CHK1/2), can phosphorylate p53 at these sites. Phosphorylation can also stimulate associations between p53 and histone acetyltransferases (HATs)/lysine acetyltransferases (KATs), which are crucial for the stability and activation of p53 [94]. For instance, phosphorylation of S15 can also trigger a series of other p53 phosphorylation events that contribute to p53 induction and activation, showing that S15 phosphorylation is a key event in p53 activation and stabilization [95]. It has been reported that phosphorylation of S15 leads to the dissociation of MDM2 from p53, which increases the stability of p53 [96]. In addition, ATM and ATR can phosphorylate p53 on S20, which mediates p53 stabilization in response to genotoxic stress, and ionizing radiation (IR) and ultraviolet (UV) irradiation can induce DNA damage to promote this process [97].

In addition, the functions of p53 range from "stressor" and "guardian" to "killer" depending on the type of post-translational N-terminal phosphorylation. The function of S46 phosphorylation in p53 is closely related to the killer function of p53 in inducing apoptosis, and this residue can be phosphorylated by numerous candidate kinases, such as homeodomain-interacting protein kinase 2 (HIPK2), p38 and dual specificity tyrosine-phosphorylation regulated kinase 2 (DYRK2) [98, 99]. The coactivators CBP and its paralog p300 play vital roles in gene transcription regulation via various mechanisms, including acetylating histones to remodel chromatin [100, 101]. Initially, p300/CBP was shown to bind to p53 to promote its transcriptional activity [102]. For instance, the interactions between p53 and MDM2 or p300/CBP are regulated by various phosphorylation events in the N-terminus of p53, which lead to simultaneous binding of one monomer of p300/CBP to tetrameric p53 to mediate p53-dependent transactivation in response to genotoxic stress [103, 104]. p53 cooperates with apoptosis stimulating protein of p53 (ASPP) to bind to and cooperate with p300, selectively regulating the apoptotic function of p53 [105, 106]. The role of N-terminal phosphorylation is to regulate the interaction between p53 and its inhibitor MDM2 or coactivators p300/CBP, and growth factor-mediated phosphorylation coordinates physiological and developmental signaling [107, 108]. These results suggest that the transcriptional coactivator p300/CBP is an important player in activating p53.

3.1.2 | Acetylation of p53 is involved in the fine tuning of cellular responses to genotoxic stress

Lysine (K) acetylation of histones is a critical epigenetic modification that influences histone structure and gene

expression [109]. The first example of protein acetylation was reported on histones in 1964 [110]. Over the following 30 years, lysine acetylation was also discovered in nonhistone proteins, such as HMG-1 [111] and tubulin [112]. However, nonhistone protein acetylation received little attention until the discovery of p53 acetylation in 1997 [104, 113–115]. Acetylation of p53 is an important post-translational modification that is essential for its activation and occurs via a reversible enzymatic process [116–118]. The same lysine residues in the C-terminus of p53 can be modified by either acetylation or ubiquitination (similar to neddylation and methylation), and these modifications are mutually exclusive and have different effects on p53 regulation [119–122].

Six p53 lysine residues within the CRD (K370, K372, K373, K381, K382, and K386) can be targeted by MDM2 [90]. These modifications lead to activation of the transcriptional activation activity of p53 and boost its stability. p300/CBP are transcriptional coactivator proteins that play a dual role in regulating p53 function. For example, the interaction between p300 and either p53 or E2 promoter binding factor 1 (E2F1) has a significant impact on early cell cycle progression, suggesting a critical role for p300 in cooperation with the pathways of growth arrest regulated by E2F and p53 [123]. In addition, the 6 modification sites (K370, K372, K373, K381, K382, and K386) facilitate the ubiquitination of p53 by MDM2, which decreases the p53 level in the presence of genotoxic stress [124]. Similar to MDM2 and Pirh2, Dicer is usually considered a major cellular ribonuclease that post-transcriptionally modulates gene expression by processing microRNAs (miRNAs) [125] and small interfering RNAs (siRNAs) [126]. Unexpectedly, upon binding of unacetylated p53, Dicer is recruited to the promoters of p53 target genes, where it represses p53-mediated transcriptional activation [127]. Moreover, p53 acetylation in the C-terminal region, which contains target residues for ubiquitination, protects it from degradation. K320, located in the TD, can be acetylated by P300/CBP-associating factor (PCAF) after DNA damage, and this acetylation is beneficial for cell survival, as it boosts the expression of p53-controlled cell cycle arrest-related target genes, such as cyclin-dependent kinase inhibitor 1A (*CDKN1A*, commonly called p21) [128, 129].

Uniquely, K120-acetylated p53 accumulates in mitochondria, which is thought to negatively regulate apoptosis by affecting the BAK/Mcl-1 interaction [130]. Located in the p53 DBD, another extensively studied p53 acetylation site is K120 on the DBD, which is catalyzed by 3 members (Tip60, males absent on the first [MOF], and monocytic leukemia zinc finger protein [MOZ]) of the MYST HAT family. Tip60 acetylates p53 at K120 to selectively induce the expression of proapoptotic genes (like *PUMA* and *Bax*), but not cell cycle arrest genes [131]. In addition, K120 and K164 are located in the p53 DBD, the most common region for p53 mutations in malignant solid tumors, indicating that they might be connected to the function of p53 in cancer [132]. K120 mutation was found in Ewing's sarcoma and esophageal squamous cell carcinoma (ESCC) cells, while a K164 mutation was discovered in glioblastoma (GBM) [133] and bladder carcinoma [134]. These data indicate the key role of p53 acetylation in its tumor suppressor activity.

3.1.3 | p53 methylation contributes to its tumor suppressor activity

Lysine and arginine (R) residues in p53 can be methylated, and recent accumulating studies have shown that p53 methylation occurs during the DNA damage response (DDR) [135–137]. Additionally, some lysines on p53 can also be methylated. It was found that firstly reported the methylation of p53 lysine at K372by SET7/9 [138]. This modification can stabilize p53 and restrict it in the nucleus. Meanwhile, it is also associated with enhanced transcription of some target genes like *p21* [139]. Recently, methylation of p53 has emerged as an important modification that affects its function in various processes, such as cell cycle arrest, DNA repair, senescence, apoptosis, and tumorigenesis [139]. Whether p53 is activated or suppressed depends on the location of the modification and the number of methyl groups attached [140]. Protein arginine N-methyl transferase 5 (PRMT5) was first shown to methylate p53 at several arginine residues (R333, R335, and R337) in the TD [135]; these modifications specifically control the functions of p53 in cell cycle arrest and are suggested to inactivate p53 during lymphomagenesis [141, 142]. Three different lysine methyl transferases (KMTs) can monomethylate p53, and at least 2 KMTs can di-methylate p53 [143].

Mono-methylation of p53 by SET and MYND domain-containing protein 2 (SMYD2) at K370, which was shown to repress p53-mediated transactivation, decreases the binding of p53 to the promoters of its target genes, such as *p21* [144]. Mono-methylation at K372 by SET7/9 boosts the activation of p53 downstream target genes, but mono-methylation of K370 by SET8 inhibits p53 transcriptional activity [145, 146]. Interestingly, lysine-specific demethylase 1 (LSD1) selectively removes this second methyl group, thus inhibiting p53 function by disrupting the association of p53 with p53 binding protein 1 (53BP1), which contributes to these effects [147, 148]. Thus, p53 contributes to maintaining DNA methylation homeostasis and clonal homogeneity, which may benefit its anticancer activity.

3.1.4 | Localization of p53 via p53 SUMOylation

Most antiapoptotic functions of p53 are performed in the nucleus, especially under steady-state conditions [149, 150]. p53 is normally SUMOylated at a single site, K386, by protein inhibitor of activated stat (PIAS) family members and TOP1 binding arginine/serine-rich protein (Topors) [151, 152]. When the C-terminal nuclear export signal (NES) of p53 is masked by its unmodified C-terminal region, p53 remains in the nucleus. Moreover, SUMOylation of p53 releases it from the chromosomal region maintenance 1 (CRM1) Huntington-EF3-PP2A subunit-HEAT9 loop to disassemble the transport complex and promote the translocation of p53 to the cytoplasm [153]. Thus, the nuclear export of p53 can facilitate cellular proliferation through the loss of its growth inhibitory function. Cytosolic p53 performs a non-transcriptional function by interacting with B cell lymphoma/leukemia (BCL)-2 and then counteracting the antiapoptotic function [154]. In addition, p53-Bcl-2 binding depends on p53 SUMOylation [155], and an abundance of cytoplasmic p53 is clinically associated with poor prognosis and disease progression to hormone-resistant status [156].

3.1.5 | Ubiquitination and neddylation

Ubiquitin is a 76-amino acid small protein with a molecular mass of ~8.5 kDa. After a hierarchical cascade of enzymatic reactions, which are catalyzed by an E1 ubiquitin-activating enzyme, an E2 ubiquitin-conjugating enzyme, and an E3 ubiquitin ligase, ubiquitin can be transferred to specific substrates, resulting in monoubiquitinated or polyubiquitinated substrates via a process named ubiquitination [157]. The major role of this modification is to target substrates for proteasomal degradation; however, ubiquitination can also regulate protein localization, protein activity, and protein-protein interactions (PPIs) [158, 159]. Ubiquitination plays a vital role in p53 regulation. The first report about p53 ubiquitination came from the Howley laboratory in 1993 and showed that the oncogenic human papillomavirus (HPV)-16 E6 protein and the E6-AP complex could ubiquitinate p53 [160].

MDM2 is the major E3 ubiquitin ligase and negative regulator of p53. MDM2 can modify p53 at six lysine residues within the CTD (K370, K372, K373, K381, K382, and K386) [161]. High levels of MDM2 activity promote the polyubiquitination and nuclear degradation of p53 (Figure 3A), whereas low levels induce its mono-ubiquitination and nuclear export [162]. However, in the cytoplasm, p53 can perform transcription-independent roles [163]. Interestingly, MDM2 itself is a transcriptional target of p53. Thus, p53 and MDM2 can form a double-negative regulatory loop [164, 165]. Notably, MDM2 can also inhibit p53 transcriptional functions by directly binding to p53 at the target DNA site. The E3 ligase activity-lacking homolog of MDM2, MDMX (or MDM4), can dimerize with MDM2 and strengthen this inhibition [88]. In addition to MDM2, other E3 ligases can target p53. Tripartite motif 69 (TRIM69) can interact with p53 and induce its ubiquitination [166]. During tumorigenesis, TRIM69 expression is inhibited, leading to p53 activation and cataract formation. Another TRIM family member, TRIM59, is upregulated in gastric cancer [167]. TRIM59 interacts with p53 and induces its ubiquitination and degradation, thus promoting gastric carcinogenesis. In addition, UBA And WWE Domain Containing E3 Ubiquitin Protein Ligase 1 (UREB1), constitutive photomorphogenic 1 (COP1), Hsc70-interacting protein (CHIP) and Pirh2 directly ubiquitinate p53 to target it for proteasomal degradation [168, 169]. In addition, 2 other ubiquitin-like proteins, named SUMO and neural precursor cell expressed developmentally downregulated protein 8 (NEDD8), can be conjugated to p53 lysines via a mechanism similar to that of ubiquitination [170, 171]. The 2 related processes are named SUMOylation and neddylation. Unlike ubiquitination, however, SUMOylation and neddylation seem can affect p53 stability or localization [171]. For example, PIAS family members and Topors can SUMOylate p53 at K386 to prevent the access of p300 to this C-terminal lysine [151, 172], which inhibits the transcriptional activation function of p53. Neddylation of p53 by MDM2 (at K370, K372, and K373) or FBXO11 (at K320 and K321) inhibits p53 transcriptional activation activity [173, 174].

3.1.6 | Other modifications

p53 can also undergo other modifications in addition to those mentioned above. O-GlcNAcylation of p53 at S149 promotes its stabilization and activity upon DNA damage [175, 176]. This modification is associated with decreased T155 phosphorylation and stabilizes p53 in a ubiquitination-dependent manner. When DNA damage occurs, poly (ADP-ribose) polymerase-1 (PARP-1) mediates the ADP-ribosylation of p53 to respond to the stress. However, this regulation of p53 by PARP1 is damage type-dependent [176]. In 2018, p53 was found to be hydroxylated at proline (P) 359 by PHD3 [177]. P359 hydroxylation forms a binding site for USP7/10, which can deubiquitinate p53 to increase its stability [178, 179]. Recently, Liu *et al.* [180] identified three novel sites for β-hydroxylation in p53 (K120, K319, and K370), which is catalyzed by CBP. β-hydroxylation of p53 reduces its acetylation and the expression of its downstream genes *p21* and *PUMA*,

thus weakening p53-dependent cell growth arrest and apoptosis.

As mentioned previously, p53 has multiple sites that may be subject to different types of modifications, which raises questions about the relative importance of modifications at individual sites in regulating p53 function (Figure 3B). In most cases, the impact of moving to a location is not significant. There is a large interaction between these changes, and they can be classified according to several criteria. These include homogeneous modification strands (where one modification affects another modification of the same type) and heterogeneous modification strands (chains between different modification types), as well as narrow modification strands (where one modification affects another in its local area). And deleted modification strings (strings with a certain distance between modifications), and cooperative modification crosstalk (where one modification promotes or enhances the effect of another) versus antagonistic modification crosstalk (where one modification antagonizes the effect of another). Examples of these different crosstalk types are depicted in Figure 3.

Many proteins are involved in the regulation of p53 modifications, including modification writers, readers, and erasers. However, there may be regulators that have yet to be discovered. It is important to understand how these proteins are regulated during various physiological and pathological processes. Answering these questions will provide insights into the functional mechanisms of p53 and improve clinical applications of targeting p53 modification pathways. Currently, there are several promising small molecules targeting the p53 modification pathway to treat diseases. Targeting this pathway is difficult due to its complexity, but there are many suitable enzymes that can be targeted. In addition, p53 mutations are common in a variety of diseases, especially cancer. Some mutations disrupt normal changes, such as the K120 mutation, which eliminates acetylation [181]. On the other hand, some mutations can lead to new changes. Targeting the post-translational modification (PTM) pathway may help regulate cellular stress responses in mut-p53 [122]. However, this area remains poorly understood and requires more attention. We hope that future studies will identify additional drug candidates targeting WT and mut-p53 modification pathways.

3.2 | p53 dynamics in response to multiple stress stimuli

The dynamics of p53 expression combined with the stability of the target mRNA influence the dominant gene networks in the response to genotoxic stress. Researchers have recently found that IR induced a pulsed pattern of p53 expression, whereas UV irradiation induced a sustained pattern of p53 activation. The pulsed pattern of p53 induction tended to result in nonlethal and reversible outcomes for the cell, whereas the sustained pattern resulted in cell death or senescence [182, 183]. The p53-activating molecule nutlin-3a can convert the radiation-associated pulsed p53 pattern into a sustained expression pattern, which changes the cell survival outcome associated with the pulsed pattern into a senescence outcome [184]. Moreover, prolonged challenge with low-dose doxorubicin (Dox) triggers sequential p53 pulses. Upon exceeding an effective threshold, proapoptotic genes are transactivated, resulting in a terminal pulse that induces apoptosis at a rate comparable to that of acute high-dose treatment [47]. Thus, these studies collectively suggest that the pattern of p53 expression plays a role in determining whether apoptosis or cell cycle arrest occurs in response to a given stress (Figure 4).

Another fundamental question is whether p53 pulses cause dynamic expression of its target genes, impacting cell fate [47, 185]. Hafner and colleagues systematically analyzed the pattern of p53 DNA binding and the transcriptome changes accompanying DNA damage-induced p53 oscillation [185–188]. Surprisingly, DNA binding of p53 revealed a pulsatile pattern that was uniform across all genomic loci; however, identical p53 oscillation activated target genes that exhibited multiple distinct expression dynamics, indicating that posttranscriptional mechanisms are responsible for the differences in gene expression dynamics [77, 189]. Indeed, a recent study demonstrated that the different decay rates of target mRNAs resulted in p53 oscillation-associated target gene expression dynamics in the form of either a pulsatile or sustained p53 level [189]. This finding suggests that p53 pulses coordinate target gene dynamics to determine cell fate [190, 191].

4 | STRUCTURE AND CHARACTERISTICS OF MUT-P53 IN CANCERS

TP53 is located on the short arm of human chromosome 17 (17p13.1) and consists of 11 exons and 10 introns. WT p53 has 393 amino acid residues. The categories of p53 mutations and their characteristics affect how p53 performs its major function as a homo-tetrameric TF with a multidomain structure. p53 contains 6 major domains, namely, 2 intrinsically disordered N-terminal TADs, a proline-rich domain (PRD), a central DBD upstream of a TD, and an intrinsically disordered CRD (Figure 5A); by binding to p53-responsive elements located in target gene promoters or enhancers, p53 can enable the expression of multiple genes to govern the regulation of the fate of normal and

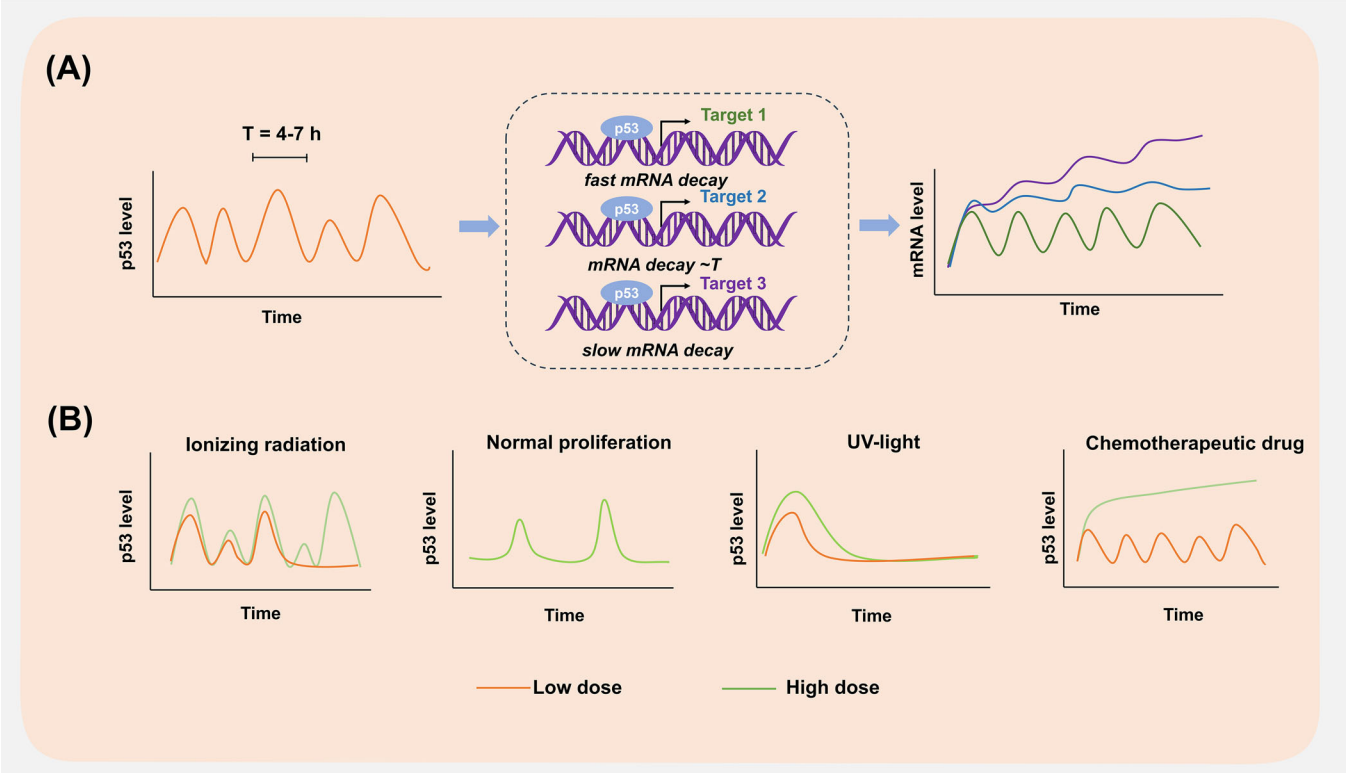

FIGURE 4 p53 dynamics are interpreted by a network of target genes. (A) Depending on mRNA stability and the timing between p53 pulses, p53 target genes may show different extents of oscillatory and increasing dynamics. mRNA decay rates can therefore act as a filter for p53 expression dynamics. (B) The dynamics of p53 accumulation are stimulus dependent. In response to DNA double strand breaks caused by IR, p53 accumulates in pulses of uniform amplitude and duration, the number of which depends on the extent of damage. Similar pulses are observed during normal proliferation due to spontaneously occurring endogenous damage. In contrast, the amplitude and duration of p53 accumulation upon UV radiation increases gradually with the damage dose. High doses of chemotherapeutic drugs like etoposide or cisplatin leads to monotonic increases in p53 levels, while low doses induce oscillatory dynamics. Data were retrieved from and based on [21, 606]. UV, ultraviolet; IR, ionizing radiation

cancer cells [79]. In addition to the full-length form dubbed p53, the *TP53* gene encodes at least 3 isoforms, named as Δ40p53, Δ133p53, and Δ160p53 (Figure 5A). These isoforms differ from full-length p53 at their N- or C-terminal regions, however, most maintain the central DBD [84, 192]. Several mechanisms have been proposed to explain presence of p53 isoforms, including alternative splicing, employment of alternative promoters, use of alternative translation start sites and proteolytic cleavage [84, 192]. At least some isoforms have been shown to modulate the activities of the full-length p53 protein, i.e., they were reported to either enhance or inhibit its actions [192]. For example, the Δ40p53 isoform was found to form oligomers with full-length p53 and increase its transactivation ability, while Δ133p53 was reported to rescue cells from full-length p53-induced apoptosis [84]. Few of the reported activities of the p53 isoforms, however, have been confirmed across different tumor types. Thus, based on current evidence, it is difficult to generalize with respect to ascribing a specific role to any of the p53 isoforms. However, *TP53* mutations occur in over 50% of human cancers [193]. In addition, mut-p53 not only exhibits loss of the tumor suppressor function of WT p53 but also acquires new functions that contribute to the progression of malignant tumors [194]. *TP53* mutations have been found in both germline (associated with Li-Fraumeni syndrome) and sporadic contexts throughout the gene [49], which predispose patients to a variety of early-onset cancers, including breast cancer, sarcomas, brain tumors, and adrenal cortical carcinomas. Somatic *TP53* mutations contribute to sporadic cancers, such as ovarian cancer, breast cancer, colorectal cancer, head and neck cancer, and lung cancer [195]. More importantly, mutations in *TP53* are correlated with poor prognosis in malignancies of the breast, bladder, and hematopoietic system [196]. Furthermore, the *TP53* mutation spectrum differs among tumors. The various types of *TP53* mutations have been the subject of recent comprehensive reviews [197, 198].

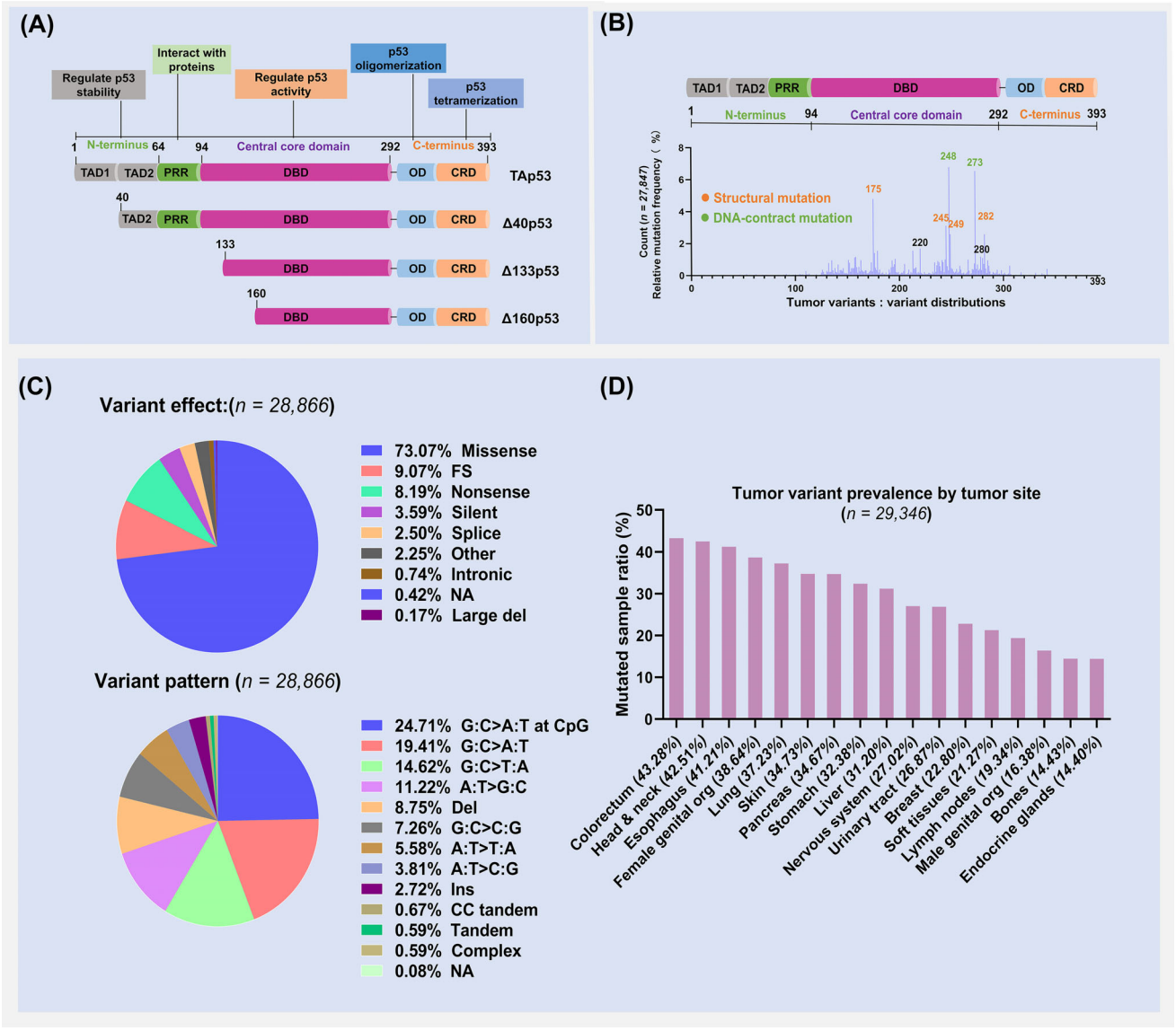

FIGURE 5 p53 structural domains, with an overview of the most frequent *TP53* mutations by tumor site, variant effects and patterns in human cancers. (A) Each p53 domain and its isoform is a target of different PTMs (alone or concomitant) that regulate p53 function. p53 interacts directly with different PTM enzymes, transcriptional cofactors, and other nuclear or cytoplasmic proteins (examples associated with a p53 interacting domain are shown in the white boxes) that modulate p53 function. (B) Graph showing the relative frequency of *TP53* missense mutations per codon (DBD-encoding codons are highlighted in faded blue boxes, residues 94-292). Highlighted in purple is codons 175, 245, 248, 249, 273, and 282 (the hotspots with the highest mutation frequencies), and codons 280 and 220. (C) The pie (right) charts show the different tumor-derived mutation types (variant effect and variant pattern) reported in the IARC *TP53* Mutation Database. (D) The bar chart shows that the frequency of TP53 mutations in tumor tissue samples from over 10,000 cancer patients and These codons code for amino acid residues critical for p53 structure and function. (Graph constructed with GraphPad 8 and data from the IARC *TP53* Database, R20, July 2019). FS, frameshift; NA, not applicable; IARC, International Agency for Research on Cancer; TAD, transactivation domain; PRR, proline-rich region; DBD, DNA-binding domain; OD, oligomerization domain; CRD, C-terminal regulatory domain; PTM, posttranslational modification

4.1 | Mut-p53 types and their spectrum in cancers

The main types of *TP53* mutation are missense mutations, truncation mutations, in-frame mutations, and splice mutations, among which missense mutations result in single amino acid substitutions, which can confer GOF activity during tumorigenesis [199]. Notably, approximately 80% of missense mutations are clustered in the regions of *TP53* that encode the central DBD of p53,

with several recurring hotspot mutations having been observed [200] (Figure 5B). The most common hotspot missense mutation sites are R175, G245, R248, R249, R273, and R282; such mutations account for ~25% of all *TP53* mutations and have high clinical significance [201, 202] (Figure 5B). In contrast, mutations outside of the DBD are more likely to be nonsense or truncation mutations (~67%) than missense mutations [203, 204]. In addition, beyond the acquisition of a *TP53* mutation in one allele, the second allele is lost in most tumors by deletion or copy neutral loss of heterozygosity [79, 205]. Analysis of the International Agency for Research on Cancer (IARC) *TP53* Mutation Database (https://tp53.isb-cgc.org) showed that most substitution mutations were G-to-A transitions, followed by C-to-T transitions (Figure 5C). Proteins harboring these hotspot missense mutations can usually be classified as contact mutants (R248Q and R273H), which make direct contact with DNA, or structural mutants (R175H, G245S, R249S, and Y220C), in which the structure of the DNA-binding interface is maintained [75, 206]. More interestingly, not all mutations have equivalent effects. For example, contact mutants have a lower affinity for p63 or p73 than conformational mutants [207, 208]. Mutations in the N-terminal TAD result in truncated forms of p53, which can activate apoptotic target genes [209]. However, most mutations occur in the DBD of WT p53 and lead to its functional inactivation. Different single amino acid substitutions of the same residue also have different effects. For example, the p53 R175C mutant induces both cell cycle arrest and apoptosis, and the p53 R175P mutant induces only cell cycle arrest, whereas the p53 R175D mutant loses both functions [11, 210]. It is important to be reminded that low frequency of p53 mutation result from a deactivation of p53 by other means in such cancer types, such as p53 mutation N236S increases collagen contraction and upregulates Cancer-associated fibroblasts-associated markers, including C-X-C motif chemokine ligand 12 (CXCL12), fibroblast growth factor 10 (FGF10), and alpha-smooth muscle actin (α-SMA), thereby promoting tumor progression through targeted activation of the signal transducer and activator of transcription 3 (STAT3) signaling pathway [211]. Additionally, HPV inhibiting p53 function through the E6 and E7 viral oncoprotein [212, 213]. In addition, *TP53* mutation may increase the structural instability of p53 and expose adhesion sequences wrapped in its hydrophobic core to the protein surface, which drives the formation of p53 aggregates [214]. Aggregates of mut-p53 have been detected in high-grade serous ovarian, colorectal, and prostate cancers and result in loss of the tumor-suppressive function of WT p53 or GOF to promote tumor development [214, 215]. More importantly, mut-p53 can co-aggregate with p63 and p73, preventing p63 and p73 from entering the nucleus to perform transcriptional regulatory functions [216].

On the other hand, several lines of evidence suggest that the *TP53* mutational spectrum differs among tumors [217, 218]. *TP53* mutations are prevalent in tumors [219], but different tissues and organs have different *TP53* mutation spectra [220, 221]. *TP53* mutations were commonly found in the colorectum (43.28%), head and neck (42.51%), esophagus (41.21%), female genital org (38.64%), lung (37.23%), skin (34.73%), pancreas (34.67%), stomach (32.38%), liver (31.20%), nervous system (27.02%), urinary tract (26.87%), breast (22.80%), soft tissues (21.27%), lymph nodes (19.34%), male genital org (16.38%), bones (14.43%), endocrine glands (14.40%) in the IARC *TP53* Mutation Database (Figure 5D).

4.2 | Mechanisms of mut-p53 GOF in the cancer process

The majority of *TP53* mutations found in cancers lead to a loss of the ability to bind to specific DNA sequences and activate the transcription of p53 target genes and thus loss of tumor suppressive function. However, it is worth noting that approximately one-third of cancer-associated mutants still retain some level of p53 transcriptional function, although it may be limited or altered [222]. Additionally, these mutations often block tetramerization, translating into loss of function (LOF) with p53 mutations in the oligomerization domain (OD). p53 proteins with mutations in the DBD exhibit diverse degrees of functionality and, consequently, different pathological relevance [199] (Figure 6). In addition to being critically associated with LOF, p53 mutations in the DBD commonly occur in a single allele. Thus, stage I tumors are heterozygous, carrying both WT p53 and mut-p53 alleles [29]. Although WT p53 is still expressed, the DNE of mut-p53 over WT p53 is observable and can be explained by the formation of hetero-tetramers (a WT p53 dimer plus a mut-p53 dimer) without transcriptional activity [11]. WT p53 and mut-p53 share the majority of regulatory factors but have different roles. Regulation of the molecular chaperone machinery has been found to be essential for the stability of both mut-p53 and WT p53 in various studies. In fact, stabilization of mut-p53 is a prerequisite for its oncogenic GOF phenotype. The hyperstability of mut-p53 in cancer cells had previously been explained by the lack of a negative feedback loop between mut-p53 and MDM2 [11, 199]. However, mice engineered to express mut-p53 proteins, either with or without the WT allele, were found to show high levels of mut-p53 protein expression only in tumors, not in normal tissues [12]. In addition, in a mouse model with mutated p53 response elements in the MDM2 P2 promoter, p53 was still degraded, suggesting that the MDM2-p53 negative feedback loop is dispensable for p53 stability [182]. Therefore, in malignant

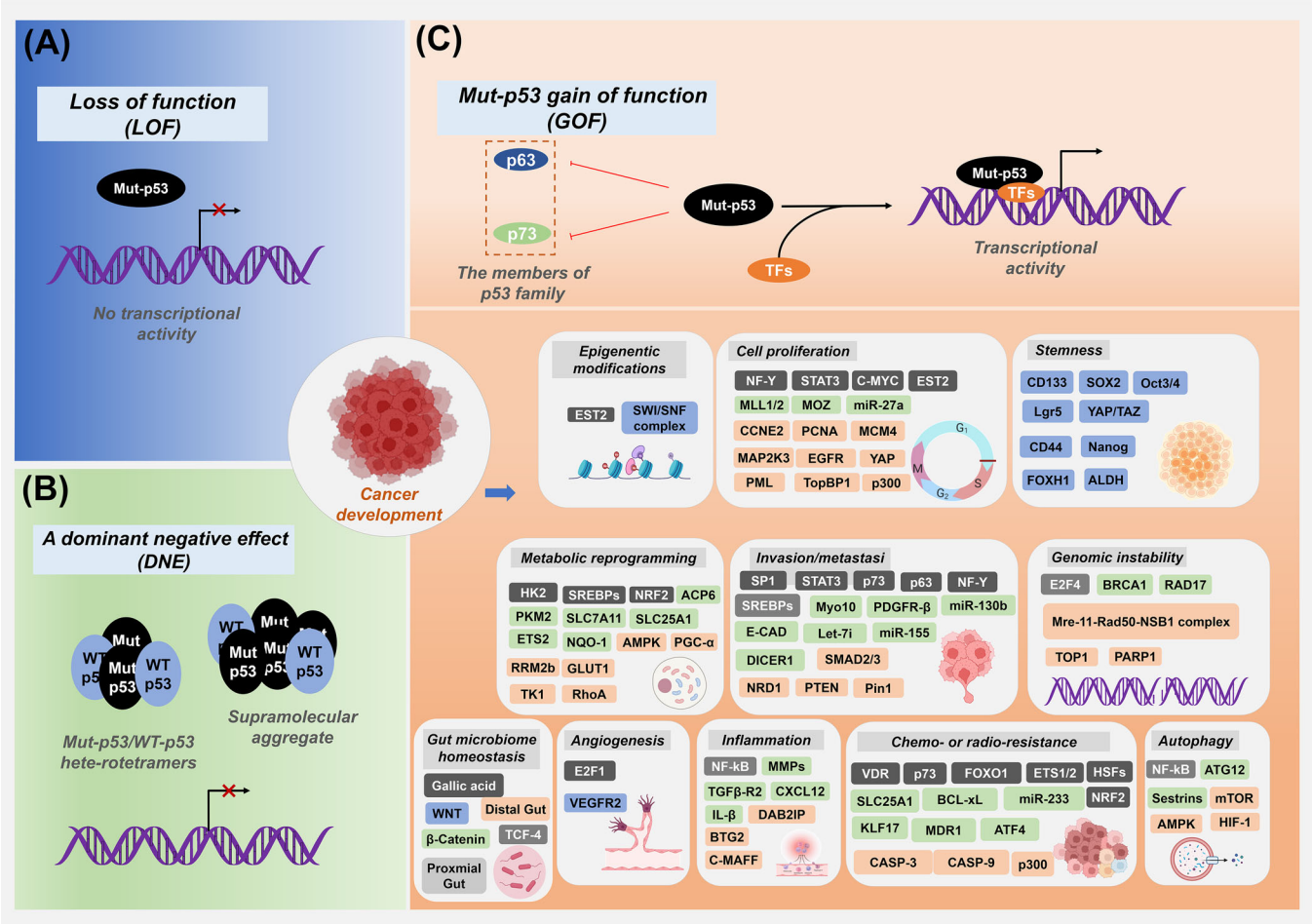

FIGURE 6 Functional activities of mut-p53 in cancers. (A) In general, p53 mutations lead to loss of DNA-binding ability and impairment of the p53 response (loss of function, LOF). (B) A DNE of mut-p53 over WT p53 occurs through the formation of hetero-tetramers and supramolecular aggregates with WT p53 [18]. (C) Mut-p53 GOF activities impact multiple hallmarks of cancer cells, affecting chromatin structure, transcriptional regulation, and miRNA biogenesis; shaping the proteome; and rewiring tumor cell metabolic pathways. The impacts also encompass cytoplasmic functions and cell-extrinsic effects, namely, effects on the TME and the inflammatory response. Oncogenic GOF of mut-p53, driving tumor development and dissemination, relies on direct interactions of mut-p53 with transcription factors (TFs, dark boxes) or cofactors and other protein effectors (orange boxes), altering their enzyme activity to induce cell stemness (blue boxes), or on transcriptional modulation of target genes (light boxes). Data were retrieved from and based on [8, 62, 72]. LOF, loss of function; GOF, gain of function; DNE, dominant negative effect; TF, transcription factor; HIF-1, hypoxia-inducible factor-1; mut-p53, mutant p53; TME, tumor microenvironment; WT, wild-type; miRNA, microRNA

cells, there must be additional mechanism(s) to stabilize mut-p53. For instance, mut-p53 binds to diverse TFs and cofactors, such as nuclear factor Y (NF-Y), p73, nuclear factor erythroid 2-related factor 2 (NRF2), and E26 avian erythroblastosis virus transcription factor-1 (Ets-1), and augments the transcription of their target genes (Figure 6). Along with tumor progression, loss of heterozygosity is commonly observed and is associated with GOF resulting from sporadic or inherited p53 mutations. GOF can be manifested through interactions of mut-p53 with various TFs or cofactors, including nuclear factor-κB (NF-κB), NRF2, hypoxia-inducible factors (HIFs), and p300/CBP. For instance, mut-p53 hetero-oligomerizes with p63 or p73, blocking their tumor suppressor activity by suppressing their transcriptional activity or inducing the transcription of noncanonical genes [79].

Several mechanisms have been proposed to contribute to mut-p53 GOF activity, which is involved in multiple biological processes: cell proliferation, cell stemness, metabolic reprogramming, inflammation, gut microbiome homeostasis, angiogenesis, genomic instability, autophagy, invasion/metastasis, and chemoresistance or radio-resistance (Figure 6). Activation of the mut-p53 transcription complex significantly induces the expression of multiple genes, which in turn plays critical roles in cell metabolism, tumorigenesis and many other processes. In addition, mut-p53 interacts with other cellular pathways and regulates various biological processes.

4.2.1 | Induction of cell proliferation by mut-p53

p53 plays a critical role in suppressing cancer cell proliferation through different mechanisms, such as cell cycle arrest, senescence, and apoptosis [75]. In contrast, mut-p53 disrupts cell cycle control, leading to enhanced proliferation. Indeed, the idea that p53 GOF accelerates cell proliferation is well established [45, 223]. In studies aimed at understanding the mechanism leading to accelerated proliferation, it was shown that tumor-derived p53 mutants interact physically with the master cell cycle regulator NF-Y. These protein complexes can increase DNA synthesis in response to DNA damage through aberrant upregulation of NF-Y cell cycle-related target genes, such as cyclin/CDK1 kinase complexes [224]. It is worth mentioning that these genes are clustered with other cell cycle control genes and that the set is annotated as a "proliferation cluster" [225]. In a subsequent study, it was found that mut-p53 interacts with yes-associated protein (YAP) and that together, they form a complex with NF-Y, which then interacts with the regulatory regions of the cyclin A, cyclin B and CDK1 genes [226]. This event was further established in a genome-wide analysis showing that p53 with GOF recognizes the promoters of the genes encoding cyclin A (i.e., *CCNA2*), which is necessary for origin firing, and CHK1, which is required for preventing replication fork collapse, and transcriptionally activates their expression in a cell cycle-dependent manner by occupying their upstream regulatory sequences [227].

Mut-p53 was also found to trigger the activation of noncoding effectors, such as the circular RNA circPVT1 and miR-497-5p, leading to uncontrolled proliferation through abnormal enhancement of the expression of cell cycle regulatory genes. This effect is regulated through the mut-p53/YAP/TEAD complex via its regulatory region [228]. On the other hand, mut-p53 was shown to suppress the expression of miR-27a, resulting in augmented cell proliferation due to enhanced epidermal growth factor receptor (EGFR) signaling, resulting in activation of the extracellular signal-regulated kinase (ERK) pathway [229]. In addition, various mut-p53 forms were shown to bind and activate STAT3, leading to increased invasion and tumor growth in colorectal cancer [230]. In addition to affecting signaling pathways, mut-p53 was shown to regulate different chromatin regulators, including the methyltransferases mixed lineage leukemia 1 (MLL1) and mixed lineage leukemia 2 (MLL2) and the acetyltransferase MOZ. This regulation was shown to globally affect histone modifications and to promote the proliferation of cancer cells [231]. Thus, it may be concluded that mut-p53 not only affects cell signaling and the transcription of specific genes but also may underlie the global chromatin changes in cancer cells, which facilitate their malignant phenotype.

4.2.2 | Mediation of cell metastasis and invasion by mut-p53

p53 plays a crucial role in suppressing cancer cell migration, invasion, and metastasis [232–234]. In contrast, promoting cancer metastasis is a well-known GOF activity of mut-p53. Mice with knock-in of p53 mutants, such as R273H and R175H, develop larger numbers of metastatic tumors than $p53^{-/-}$ mice, providing clear evidence of the role of mut-p53 in promoting tumor metastasis in vivo [48, 49]. Mut-p53 has been reported to promote metastasis through different mechanisms. One important mechanism is the promotion of epithelial-mesenchymal transition (EMT). Mut-p53 transcriptionally represses miR-130b to upregulate ZEB1, a key EMT-related TF, to promote EMT and cancer cell invasion [235]. Mut-p53 also promotes EMT and metastasis by upregulating the EMT-related TF Twist1 [236] and interacting with the p53 family member p63 to form a complex with Smad2 in order to activate TGF-β signaling, which is essential for EMT [237]. In addition to EMT, other mechanisms include the modulation of cell motility and the extracellular matrix (ECM). For instance, mut-p53 promotes metastasis by regulating SUMOylation of the small GTPase Rac1 to induce its activation, which plays a vital role in cell motility and cancer metastasis [39]. Mut-p53 promotes tumor cell invasion and motility by enhancing the interaction between integrin A5b1 and Rab-coupling protein (RCP), an essential regulator of endocytic trafficking, which in turn promotes the recycling of EGFR and the protein tyrosine kinase mesenchymal-epithelial transition factor (MET) [238, 239]. Mut-p53 also promotes RCP-dependent endocytic trafficking in neighboring cancer cells via exosome secretion, leading to the deposition of a highly pro-invasive ECM [240]. Mut-p53 sequesters p73, preventing it from forming a complex with NF-Y, thus activating PDGF receptor b (PDGFRb) signaling to promote pancreatic cancer metastasis [241]. In addition, in the R172H mut-p53 knock-in mouse model, R172H mut-p53 was found to promote tumor metastasis through an interaction with the TF E26 transformation-specific proto-oncogene 2 (ETS-2), inducing the expression of a cluster of small nucleolar RNAs (snoRNAs) [242] and upregulating the Pla2g16 phospholipase, which catalyzes the conversion of phosphatidic acid into lysophosphatidic acid and free fatty acid, both of which are implicated in metastasis [243].

4.2.3 | Mediation of genomic instability via mut-p53

Genomic instability is a hallmark of cancer. While p53, as a guardian of the genome, plays a critical role in maintaining genomic stability, mut-p53 GOF promotes

genomic instability, including chromosomal and amplification instability [244]. For instance, fibroblasts from Li-Fraumeni syndrome patients harboring missense p53 mutations, including R175H, undergo S-phase reentry after exposure to spindle depolymerizing agents that disrupt mitotic spindles, leading to the generation of polyploid cells; in contrast, S-phase reentry is blocked in p53-null fibroblasts [245]. Ectopic expression of mouse R172H (equivalent to human R175H) mut-p53 in p53-null primary mouse mammary epithelial cells leads to significant centrosome amplification and an increased frequency of aberrant mitosis [246]. In the pancreatic ductal adenocarcinoma mouse model, expression of R172H mut-p53 and KRAS (G12D) cooperatively lead to the development of invasive and metastatic carcinomas with a high degree of genomic instability manifested by nonreciprocal translocations without apparent telomere erosion [247]. Proper DDR and DNA repair functions are crucial for maintaining cellular genomic stability. Mut-p53 can induce genomic instability by impairing the DDR and DNA repair. R248W and R273H mut-p53 can bind to the nuclease Mre11 and prevent the association of the Mre11-Rad50-NBS1 (MRN) complex with DNA double-strand breaks (DSBs), which in turn impairs ATM activation and the DDR [248]. Mut-p53 interacts with the E2F4 and binds to the promoter regions of breast cancer 1 protein (BRCA1) and RAD17 checkpoint clamp loader component (RAD17), critical proteins involved in DNA DSB repair, to repress BRCA1 and RAD17 expression and impair DNA repair [249]. Mut-p53 was also reported to enhance the association of the DNA repair protein PARP1 with chromatin and increase the levels of the nuclear replication proteins minichromosome maintenance 4 (MCM4) and proliferating cell nuclear antigen (PCNA), which in turn impairs DNA repair and simultaneously promotes DNA replication to cause genomic instability [250]. In addition, other mechanisms have been suggested to contribute to the role of mut-p53 GOF activity in inducing genomic instability. For example, the p53 family member p73 plays a vital role in the spindle assembly checkpoint by directly interacting with budding uninhibited by benzimidazole 1-related 1 (BubR1), a spindle assembly checkpoint protein crucial for proper centrosome maintenance and chromosomal stability, to enhance its ability to phosphorylate downstream checkpoint effectors [251]. Since mut-p53 can bind to p73 and inhibit its transcriptional activity [207], mut-p53 may impair BubR1 function, leading to a defective spindle assembly checkpoint and aneuploidy [244]. Mut-p53 also promotes the formation of cell-in-cell structures via live-cell engulfment, which interferes with the division of host cells to result in genomic instability [252].

4.2.4 | Fueling of cell de-differentiation and stemness by mut-p53

p53 promotes differentiation and suppresses the proliferation of stem cells, acting as a barrier to the formation of cancer stem cells (CSCs). In contrast, mut-p53 exhibits GOF activity to regulate de-differentiation processes and facilitate CSC maintenance [253]. It was reported that bone marrow mesenchymal stem cells in Li-Fraumeni syndrome patients are tumorigenic and can induce sarcomagenesis [254]. Similarly, accumulation of mut-p53 in progenitor-like cells in subventricular zone-associated areas of the brain leads to gliomagenesis [255]. Mut-p53 enhances the expression of colorectal CSC markers (e.g., CD44, leucine-rich-repeat-containing G-protein-coupled receptor 5 [Lgr5], and aldehyde dehydrogenase [ALDH]) by binding to the CD44, Lgr5 and aldehyde dehydrogenase 1A1 (ALDH1A1) promoter sequences in colorectal cancer cells [256]. Mut-p53 promotes the proliferation and growth of CSC-like cells. In addition, it increases the expression of CSC markers (CD133, CD44, and YAP/TAZ) in GB and breast cancer cells by regulating WASP interacting protein (WIP), which in turn stabilizes YAP/TAZ [38]. Mut-p53 also promotes aberrant self-renewal of leukemic cells. Hematopoietic stem and progenitor cells exhibit this phenotype even before their transformation via upregulation of fork head box protein H1 (FoxH1), a TF involved in the regulation of stem cell-associated genes [257].

4.2.5 | Regulation of cellular metabolic reprogramming by mut-p53

Metabolic reprogramming is a hallmark of cancer that meets the demands for energy and macromolecules to support the rapid growth and proliferation of cancer cells. While p53 plays a critical role in maintaining metabolic homeostasis in normal cells, mut-p53 GOF promotes metabolic reprogramming in cancer cells [73, 258]. Enhanced aerobic glycolysis (namely, the Warburg effect) is the most well-characterized metabolic change in cancer cells. WT p53 has been reported to inhibit the Warburg effect in cancer cells by transactivating target genes required for oxidative phosphorylation, such as synthesis of cytochrome C oxidase 2 (*SCO2*) [259], as well as genes such as TP53-induced glycolysis and apoptosis regulator (*TIGAR*) and *Parkin*, to negatively regulate glycolysis [112–114]. In contrast, mut-p53 enhances glucose uptake and glycolysis by promoting the trafficking of glucose transporter 1 (GLUT1) to the plasma membrane through activation of the small GTPase RhoA and its direct downstream kinase Rho-associated coiled-coil kinase (ROCK),

which promotes tumorigenesis, both in cultured cancer cells and in R172H mut-*TP53* knock-in mice [260]. Mut-p53 also promotes glycolysis by enhancing the expression of the glycolytic enzyme hexokinase 2 (HK2) and the phosphorylation of pyruvate kinase M2 (PKM2) [261, 262]. Mut-p53 activates the mevalonate pathway by binding to and activating the sterol regulatory element binding proteins (SREBP) TFs, which induces the expression of genes in the mevalonate pathway [263]. Mut-p53 enhances nucleotide synthesis by cooperating with ETS2 to activate multiple nucleotide metabolism genes, such as ribonucleotide reductase small subunit B (*RRM2b*), Deoxycytidine kinase (*dCK*), and thymidine kinase 1 (*TK1*), to promote tumorigenesis [264]. In addition, mut-p53 binds to and activates peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a master regulator of mitochondrial biogenesis and oxidative phosphorylation, enhancing mitochondrial function to promote cancer metastasis [265]. p53 codon 72 polymorphism (R72 or P72) influences p53 activity and is associated with cancer risk and longevity [266, 267]. Interestingly, PGC-1α activation by mut-p53 is impacted by codon 72 polymorphism; cancer cells with the R72 variant of mut-p53 show more marked increases in PGC-1α function, mitochondrial function and metastatic capability [265]. Moreover, in breast and lung tumors, stem cell-like transcription patterns were found to coincide with the abolishment of WT p53 and the presence of p53 mutations [268]. These data are consistent with the observation that WT p53 suppressed the reprogramming of mouse embryonic fibroblasts (MEFs) into induced pluripotent stem cells (iPSCs) [269–273]. Moreover, mut-p53 GOF enhanced the reprogramming efficacy and the tumorigenicity of the reprogrammed cells [274].

4.2.6 | Inhibition of the TME and immune responses by mut-p53

Cancer cells actively shape a permissive microenvironment for cancer progression. Accumulating evidence has shown that mut-p53 remodels the TME and promotes the adaptation of cancer cells to the microenvironment [275]. Mut-p53 affects the expression of various secreted proteins to remodel the TME. For instance, mut-p53 activates PKC to increase vascular endothelial growth factor (VEGF) expression to promote angiogenesis [276]. Mut-p53 forms a complex with E2F1 and binds to the promoter of inhibitor of DNA-binding 4 (ID4) to induce its expression, which in turn enhances the expression of the pro-angiogenic factors interleukin-8 (IL-8) and growth-related oncogene-alpha (GRO-α) to promote angiogenesis [277]. Mut-p53 binds to the lncRNA MALAT1 to promote the association of MALAT1 with chromatin and induce VEGF expression in breast cancer cells [278]. Mut-p53 induces the release of a pro-invasive secretome into the TME through interaction with p63 [279]. Mut-p53 facilitates premetastatic niche formation by releasing exosomes to promote integrin trafficking, which enhances the deposition of a highly pro-invasive ECM [240]. Furthermore, mut-p53 forms a complex with hypoxia-inducible factor-1 (HIF-1) that binds to the switch/sucrose non-fermentable (SWI/SNF) chromatin remodeling complex and induces the expression of a selective subset of hypoxia-responsive genes. Thus, mut-p53 enhances the HIF-1-mediated expression of certain ECM components, including type VII collagen and laminin-c2, to promote the adaptation of cancer cells to hypoxia in the TME [280]. In addition, mut-p53 protects cancer cells from the tumor-suppressive effects of interferon-β (IFN-β) secreted by cancer-associated fibroblasts (CAFs) through suppressor of cytokine signaling 1 (SOCS1)-mediated inhibition of signal transducer and activator of transcription 1 (STAT1) phosphorylation [281]. The status of p53 in cancer cells profoundly impacts the immune response, resulting in various outcomes that can impede or support cancer development [282]. It was reported that the expression of mut-p53 in human lung cancer correlates with increased programmed death-ligand 1 (PD-L1) expression, which may help to identify patients responsive to checkpoint inhibitors targeting PD-L1 [283]. nuclear factor-κB (NF-κB) plays a key role in regulating the immune response to chronic inflammation. Mut-p53 activates NF-κB signaling by promoting the nuclear translocation of p65 or inhibiting the expression of the tumor suppressor disabled homolog 2 interacting protein (DAB2IP) [284, 285]. R273H mut-p53 transcriptionally represses interleukin-1 receptor antagonist (aIL-1Ra) to sustain IL-1b signaling [286]. In addition, p53 mutations (e.g., R248W) increase exosome secretion of miR-1246 to reprogram macrophages into tumor-supporting macrophages [287]. Thus, through the mut-p53 GOF mechanism, cancer cells can reprogram macrophages and other myeloid subsets to support cancer development.

4.2.7 | Endowment of resistance to cancer therapy by mut-p53

p53 induces apoptosis, cell cycle arrest, senescence, and other biological processes to mediate the response of cancer cells to therapies. In contrast, mut-p53 GOF has been reported to promote therapeutic resistance in cancer [288, 289]. Enhanced drug efflux through upregulation of ATP-binding cassette (ABC) transporters that move drugs out of cells is an essential mechanism of multidrug resistance. While p53 suppresses the expression of the ABC transporter adenosine triphosphate-binding cassette subfamily

B member 1 (ABCB1), mut-p53 GOF results in induction of ABCB1 expression to mediate the ATP-dependent efflux of drugs from cells to promote chemoresistance [290]. Mechanistically, mut-p53 is recruited to the ABCB1 promoter by interacting with E26 oncogene homolog 1 (ETS1) to activate ABCB1 transcription [291]. Mut-p53 interacts with NF-Y to induce the expression of ephrin-B2, a ligand of the ephrin receptor tyrosine kinases, which in turn upregulates the expression of the ABC transporter adenosine triphosphate (ATP)-binding cassette efflux transporter G2 (ABCG2) to promote chemoresistance [292]. Cytochrome P450 (CYP450) family members are critical enzymes in drug metabolism, mediating the process of drug oxidation. Specific forms of mut-p53 (e.g., R282W) induce CYP450 enzyme 3A4 (CYP3A4) expression to promote resistance to several chemotherapeutic drugs metabolized by CYP3A4 [293]. Mut-p53 also promotes chemoresistance by inhibiting apoptosis and autophagy. Mut-p53 binds to p63 and p73 and represses their transcriptional activity to inhibit apoptosis induced by chemotherapeutic agents [207, 294]. Mut-p53 interacts with AMPK-α to inhibit AMPK signaling, in turn activating mammalian target of rapamycin (mTOR) to suppress autophagy [295]. Furthermore, mut-p53 suppresses autophagy by forming a complex with the p50 subunit of NF-κB, which binds to the promoter of the autophagy-related gene autophagy related 12 (*ATG12*) to suppress its expression [296]. Mut-p53 also regulates miRNA expression to promote chemoresistance. For instance, R175H mut-p53 induces the expression of miR-128-2, which targets the TF E2F5 to upregulate p21, inhibit apoptosis and confer resistance to chemotherapeutic agents [297]. Furthermore, some forms of mut-p53 (e.g., R175H) downregulate miR-223 expression in cancer cells to induce chemoresistance by binding to the miR-223 promoter to reduce its expression via the transcriptional repressor zinc-finger E-box binding homeobox 1 (ZEB-1), which in turn increases stathmin-1 expression. This oncoprotein confers chemoresistance partially by regulating microtubule dynamics [298].

4.2.8 | Suppression of autophagy via mut-p53

Autophagy is widely recognized as a significant biological event that plays a role in both cancer cell proliferation and drug responses. Thorough analysis of the scientific literature reveals the reciprocal interplay between mut-p53 and autophagy regulation. The current accepted view is that mut-p53 suppresses autophagy. This view was initially illustrated by studying the effects of overexpressing 22 different p53 mutant variants on autophagy in p53-null colon cancer cells [299]. Reintroduction of various p53 mutants, such as A161T, S227R, E258K, R273H/L, and R273L but not p53 P151H and R282W, showed a strong association with efficient suppression of basal macro-autophagy. Reintroduction of other mutants, such as P98S, K120D, V143A, R175C, R175D, and R175H, exhibited weaker suppressive effects or even increased macro-autophagy in certain contexts [300]. This finding led to the realization that certain p53 mutants may have negative effects on autophagy. A common characteristic of p53 mutants is their cytoplasmic localization, which is likely accompanied by LOF to promote transactivation-dependent stimulation of autophagy [301]. Supporting finding, it was later discovered that mut-p53inhibits the formation of autophagic vesicles and their fusion with lysosomes by repressing the transcription of key downstream p53-responsive autophagy-related genes, including beclin 1 (*BECN1*), damage-regulated autophagy modulator 1 (*DRAM1*), and *ATG12*, as well as tuberous sclerosis complex subunit 1 (*TSC2*), single dominant gene (*SEN1/2*), and *p-AMPK*, resulting in blockade of autophagy [300]. It is important to note that both deletion and missense mutations of p53 can substantially interfere with mTOR signaling, while an increased association of Rheb with lysosomal membranes promotes mTORC1 complex activity [300].

4.2.9 | Triggering of angiogenesis via mut-p53

Angiogenesis plays a critical role in both physiological homeostasis and disease pathogenesis. It is defined as the formation of new blood vessels from preexisting vessels and has been characterized as an essential process for tumor cell proliferation and viability. Mut-p53 also promotes angiogenesis. In breast cancer, mut-p53 and E2F1 bind to the promoter of ID4 and enhance its expression. ID4 further binds to and stabilizes the mRNAs of IL-8 and GRO-α, which are pro-angiogenic factors [64]. In 2005, it was reported that mut-p53 could upregulate the activity of NF-κB [59], a TF that plays a critical role in inflammatory responses and cancer development [65]. Di Minin *et al.* [285] reported that in lung and breast cancer cell lines, mut-p53 augments the induction of NF-κB expression in response to tumor necrosis factor-alpha (TNFα), thereby promoting cancer progression. Cooks *et al.* [284] further discovered that mut-p53 prolongs the activation period of NF-κB triggered by TNFα. Therefore, mice expressing mut-p53 are prone to developing inflammation-associated colon cancer [66]. Mut-p53 can also promote the generation of an inflammatory TME by regulating the level of secreted IL-1 receptor antagonist (sIL-1Ra). Mut-p53 but not WT p53 binds to the promoter of sIL-1Ra with the corepressor musculoaponeurotic fibrosarcoma oncogene homolog F (MAFF) and suppresses sIL-1Ra expression to induce angiogenesis. Therefore, the production of the

pro-inflammatory cytokine IL-1β is not antagonized by sIL-1Ra [67].

5 | CELL-AUTONOMOUS AND NON-AUTONOMOUS EMERGING FUNCTIONS OF P53 IN THE TME

The activation of p53 and its role in inducing apoptosis and senescence is widely recognized as a crucial mechanism for suppressing tumors, known as the autonomous mechanism. However, recent evidence suggests that p53 also suppresses tumorigenesis by influencing the function and environment of transformed cells, referred to as the non-cell autonomous mechanism of tumor suppression [302, 303]. These include the following 2 main aspects: one is that p53 governs the immune response of the TME; the other is that microbiome meets cancer development in which p53 serves as a good matchmaker (Figures 7,8).

5.1 | TME

The TME is composed of various components, such as blood vessels, immune cells, CAFs, signaling molecules (cytokines and chemokines), and the ECM surrounding the tumor [304]. These components play a crucial role in tumor development, progression, and regulate tumor immune responses [305]. In recent years, significant scientific evidence has demonstrated the crucial role of mut-p53 or WT p53 in altering the secretion of proteins and signaling molecules. This section aims to highlight recent findings that the p53 tumor suppressor pathway is involved in crucial aspects of tumor immunology and in homeostatic regulation of TME immune responses (Figure 7). Specifically, we will focus on the impact of mut-p53 proteins on cancer invasion and metastasis through 4 main mechanisms: (1) modulation of the ECM components, (2) secretion of pro-inflammatory and immunomodulatory interleukins and cytokines, (3) modification of the extracellular pH, and (4) regulation of the communication between tumor and stromal cells.

5.1.1 | ECM

Cancer metastasis is a leading cause of death in cancer patients. This phenomenon involves a plethora of events resulting in ECM degradation, which allows tumor cells to invade the surrounding tissue and generate metastases [306]. Matrix metalloproteinases (MMPs), specifically MMP-2 and MMP-9 [307], are secreted or transmembrane enzymes that play key roles in the cancer invasion process by degrading multiple components of the ECM, including laminin, collagen, and fibrous proteins [308]. The role of mut-p53 in ECM remodeling is multifaceted, including cancer progression, metastasis, and the physiology and pathology of a wide range of diseases. Notably, the activity of metalloproteinases is regulated by the issue inhibitors of metalloproteinases (TIMPs) family, which consists of 4 members (TIMP 1-4) that have been reported to play important roles in cellular processes, such as cell differentiation, proliferation, and apoptosis [309]. It has been found that mut-p53 protein can inhibit the transcription of TIMP-3, which in turn will lead to an increase in the activity of secreted MMP in the ECM, resulting in tumor invasion and metastasis [310]. Interestingly, Novo *et al.* [311] found that in human melanoma cells expressing mut-p53 protein, reintroduction of WT p53 overcomes the GOF activity of mut-p53 and reduces cancer cell invasion into the ECM by inhibiting MMP-2 secretion. Furthermore, these results highlight the role of the intact WT p53 signaling pathway in preventing metastasis through distinct mechanisms involving ECM remodeling. In addition to cancer progression and metastasis as mentioned above, p53 proteins have been implicated in a variety of physiopathologic conditions. For example, mut-p53 causes dysregulation of the expression of human matrix metalloproteinase-13 (hMMP-13), a gene encoding a collagenase involved in the degradation of type IV collagen in the ECM, and plays a crucial role in the pathogenesis of rheumatoid arthritis [312]. Furthermore, it has been found that both MMP and mut-p53 expression are elevated in gestational trophoblastic diseases [313]. It is ostensible that there is an interaction between these two. Overall, these findings emphasize the potential role of mut-p53 in cancer invasion and metastasis as well as other pathological conditions through ECM remodeling, thus representing a hot topic for in-depth mut-p53-related research.

5.1.2 | Chemokines and cytokines

Numerous epidemiologic and experimental studies have addressed the observation that many neoplastic diseases are characterized by a relevant inflammatory component. Thus, the crosstalk between the inflammatory microenvironment and tumor cells has been demonstrated to be pivotal for cancer development, and for that reason, inflammation is considered one of the hallmarks of cancer [314]. The major players that are recruited into the TME when inflammation occurs constitute inflammatory cells and several biochemical inflammatory mediators, including cytokines, chemokines, interleukins, and enzymes, which strongly influence tumor development and progression. Chemokines are inflammatory effectors that belong

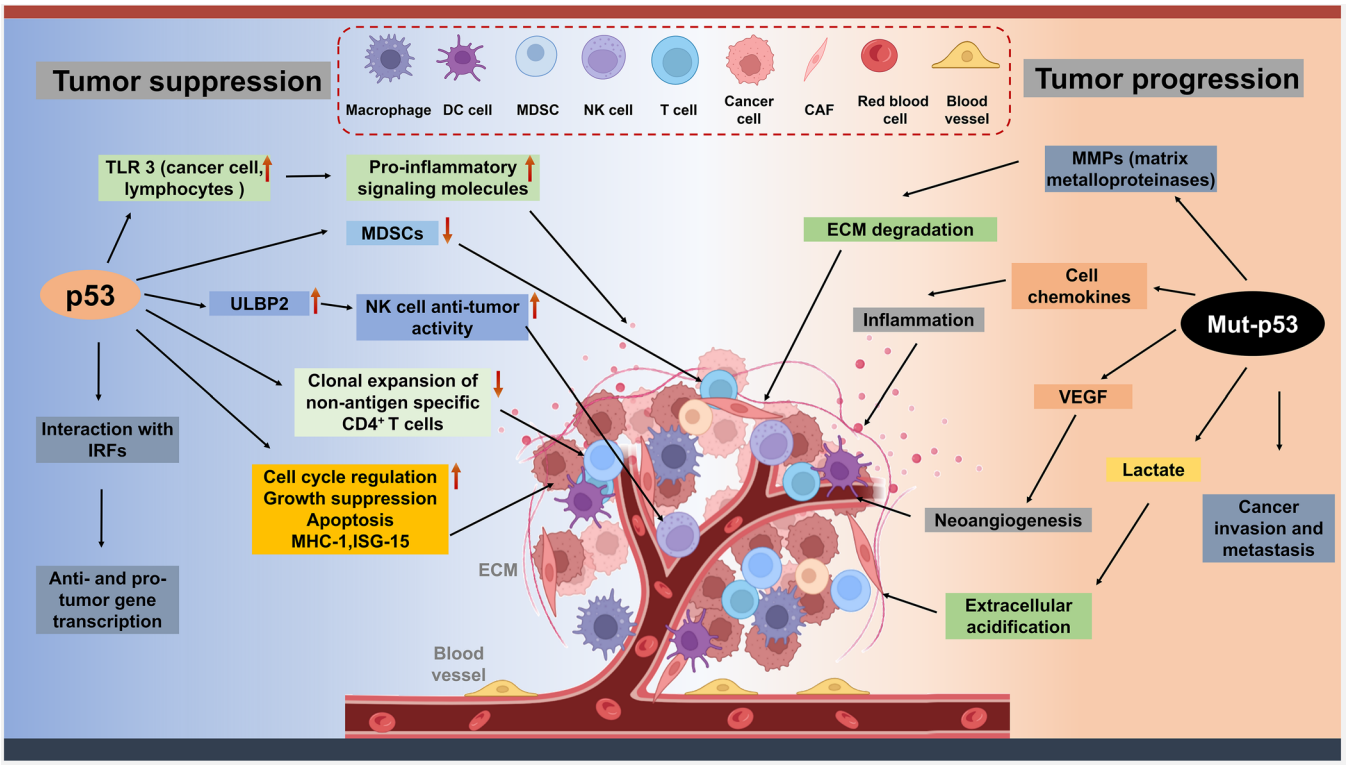

FIGURE 7 The role of p53 and mut-p53 in the TME during cancer development. The TME contains blood vessels, immune cells, CAFs, signaling molecules, including cytokines and chemokines, and the ECM that surrounds the tumor. The p53 tumor suppressor pathway plays a crucial role in tumor immunology and regulating immune responses in the TME. However, there is a contrasting function between p53 and mut-p53. Mut-p53 inhibits immune plasticity and promotes tumor progression by regulating key molecules in the TME. These molecules include ECM remodeling, pro-inflammatory and immune-regulatory cytokine secretion, vascularity, and metabolism. Mut-p53 contributes to cellular non-autonomous effects and has a pro-tumorigenic role. On the other hand, normal p53 facilitates the expression of various immune signaling molecules, such as TLR3, ULBP2, IRFs, and $CD4^+$, which are involved in the immunogenicity of cancer cells. This suggests that normal p53 may have potential oncogenic effects. Data were retrieved from and based on references [13, 206, 400]. ULBP2, UL16-binding protein 2; MMP, matrix metalloproteinase; DC, dendritic cell; MDSC, myeloid-derived suppressor cell; CAF, cancer-associated fibroblast; ECM, extracellular matrix; TLR3, Toll-like receptor 3; IRF, interferon regulatory factor; MHC, major histocompatibility complex; ISG, interferon-stimulated gene; IRF, Interferon regulatory factor; TME, tumor microenvironment; NK, natural killer; VEGF, vascular endothelial-derived growth factor

to the wide family of cytokines and can be classified into chemotactic cytokines (CC), cysteine-X-cysteine (CXC), X-cysteine (XC) and cysteine-X-3-cysteines (CX3C) based on their biochemical and functional features. Usually, during the inflammatory process, chemokines can be induced by other cytokines and are secreted by tumor or stromal cells to regulate the directional migration of leukocytes toward the site of inflammation [315]. Multiple studies have thoroughly established that chemokines have oncogenic effects. Indeed, they can promote tumor cell growth, tumor invasion, and metastasis in several cancer types [315–317]. It has been reported that chemokines can increase the metastatic potential of cancer cells by mediating their directional migration to specific distal sites, similar to the mechanism by which they control leukocyte migration [318]. In addition, they can induce the expression of MMPs and collagenases to degrade the ECM [319, 320]. WT p53 has recently been reported to inhibit both angiogenesis and cell motility by mechanistically repressing the transcription of CXC chemokines; specifically, CXCL12 [321], CXCL4 [322], CXCL5, and CXCL8 [323] have been found to be downregulated by WT p53. These findings underscore how impairment of WT p53 function might induce a pro-inflammatory phenotype through de-repression of chemokine transcription, therefore contributing to cancer invasion and metastasis. Indeed, mut-p53 proteins, unlike their WT counterparts, enhance cancer cell motility by upregulating the expression of CXCL5, CXCL8, and CXCL12 through an NF-κB-dependent pathway, highlighting a further molecular mechanism by which mut-p53 proteins exhibit oncogenic activity [323]. Indeed, NF-κB family members play pivotal roles in immunity and inflammation and have been reported to be key transcriptional regulators of chemokine expression [324–326].

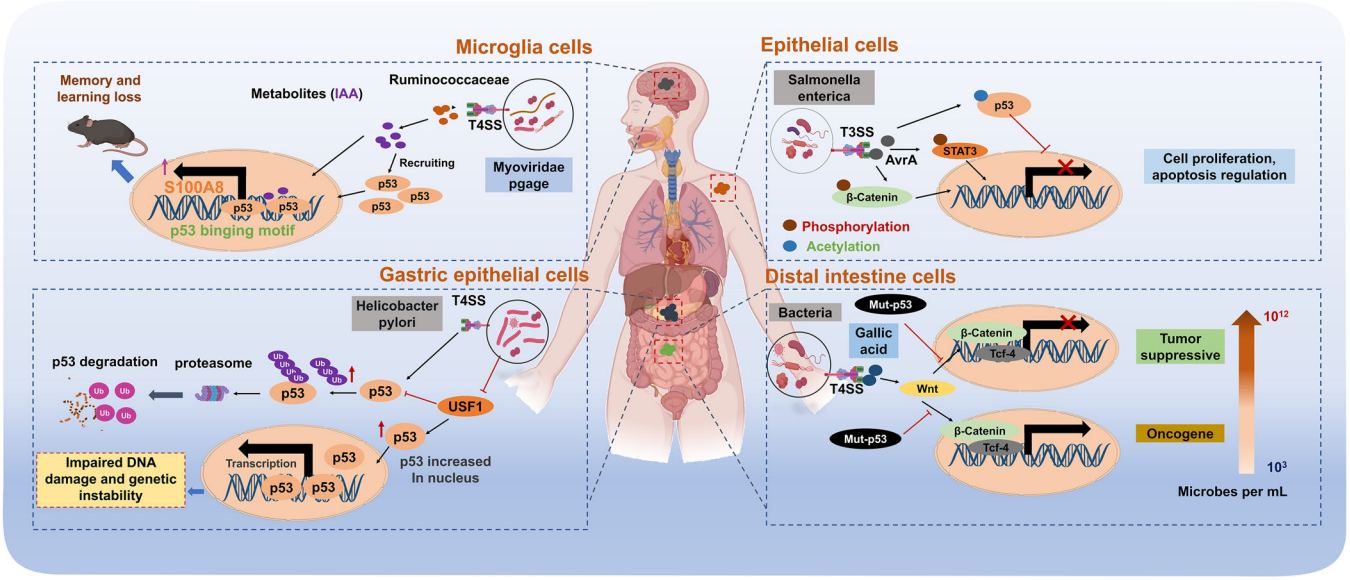

FIGURE 8 The roles of p53 and mut-p53 in the microbiome in cancer development. The gut microbiota switches the activity of p53 mutants from tumor-suppressive to oncogenic. In addition, other tissues and organs, such as brain, skin, and stomach, different microbiotas can mediate changes in p53 activity and thus participate in the development of different disease processes. Specifically, H. pylori-mediated dysregulation of USF1 and affects the protein stability of p53 and the DDR, leading to genetic instability in gastric epithelial cells. In addition, epidermal cell-derived *Salmonella enterica* also binds protein AvrA to promote cell proliferation, differentiation, and inhibit cell-cycle arrest via JAK/STAT, Wnt/β-catenin, or acetyltransferase-targeted p53 pathway, collectively resulting in tumorigenesis. Data were retrieved from and based on references [361, 607] and [363]. USF1, upstream stimulatory factor 1; STAT3, signal transducer and activator of transcription 3; TCF-4, transcription factor 4; T3SS, type III secretion system; T4SS, type IV secretion system; JAK, Janus kinase; TLRs, Toll-like-receptor genes; DDR, DNA damage response; H. pylori, Helicobacter pylori; IAA, isoamylamine

Furthermore, recent studies have shown that mut-p53 proteins induce a pro-inflammatory phenotype through both activation of the NF-κB pathway [327] and induction of NF-κB2 gene expression [188, 328]. Interestingly, some reports have revealed an alternative mechanism by which mut-p53 proteins upregulate chemokine expression, showing that they can directly bind to the CXCL1 or GRO1 promoter in SW480 colon cancer cells to activate the transcription of these genes, thus resulting in enhancement of the oncogenic potential of mut-p53 [329]. These studies support the existence of different mechanisms utilized by mut-p53 proteins to modulate the expression of inflammatory chemokines in order to maintain the inflammatory status of the TME, thus contributing to the promotion of tumor invasion and metastasis.

In addition to p53's ability to play a role in chemokines, it is also involved in the regulation of cytokines. For example, IL-1, which is normally secreted by stromal cells and infiltrating leukocytes during inflammation and immune response, has been suggested to be pleiotropic in cancer and is closely associated with malignant transformation, growth, invasion, and metastasis of tumors [330]. It has been found that sIL-1Ra has been identified as a novel target gene for mut-p53 inhibition in various cancer cell lines found to have different p53 mutants [286]. sIL-1Ra is a specific antagonist of the pro-inflammatory cytokine IL-1 that can bind to both type I and type II IL-1 receptors without transmitting any stimulatory signals, thus acting as a physiological inhibitor of IL-1 [331]. It has also been demonstrated that mut-p53 protein binds to the sIL-1Ra promoter and recruits the transcriptional co-repressor MAFF through PPIs, promoting the generation of a malignant pro-inflammatory TME [332]. This finding further supports the existence of a functional link between sIL-1Ra and mut-p53 proteins, emphasizing the impact of the pro-inflammatory phenotype on cancer progression. It also suggests that pharmacological inhibition of IL-1 may provide a promising therapeutic strategy for tumors carrying mutations in the *TP53* gene.

5.1.3 | Vasculature, metabolism, and immune aspects

Cancer is also characterized by dramatic metabolic alterations. The Warburg effect, or the preferential use of aerobic glycolysis for ATP production, is a well-known metabolic shift that occurs in cancer cells [314, 333]. Overall, accumulating evidence indicates that an acidic microenvironment increases tumor malignancy by

promoting proliferation, chemoresistance, and invasion [334, 335]. Recently, it has been clearly demonstrated that mut-p53 proteins stimulate the Warburg effect in both cultured cells and mut-p53 knock-in mice [260], unlike WT p53, which suppresses glycolysis and the Warburg effect through transcriptional regulation of genes involved in energy metabolism, including *SCO2*, *TIGAR*, glutamine synthase 2 (*GLS2*), and *Parkin* [259, 336, 337]. This metabolism-related oncogenic function of mut-p53 proteins occurs mostly via the promotion of GLUT1 translocation to the plasma membrane through activation of RhoA/ROCK signaling, thus resulting in increased glucose uptake and, consequently, increased glycolytic rate and lactate production in cancer cells [260]. Overall, these findings finally establish that mut-p53 proteins play a crucial role in the promotion of the Warburg effect in cancer cells, a phenomenon that, through both stimulation of lactate production and a reduction in the extracellular pH, makes the TME suitable for cancer cell invasion and tumor dissemination. Therefore, counteracting specific bio-elements involved in TME, acidification might be considered a valuable therapeutic strategy against cancer cells bearing *TP53* gene mutations in order to prevent the metastatic process, the main cause of death in cancer patients.

Several studies have also attributed a critical role in tumor-stroma interactions to mut-p53 proteins [13, 275, 338]. Addadi *et al.* [339] clearly showed that mut-p53 proteins exert an indirect oncogenic effect when expressed by stromal cells, providing a selective advantage to adjacent cancer cells. They observed that MEFs expressing R172H mut-p53 promoted the growth of tumors derived from PC3 epithelial cancer cells significantly more than p53-knockout (KO) MEFs. Interestingly, the same authors and others revealed that expression of R172H mut-p53 in MEFs or reintroduction of the human hotspot R175H mut-p53 protein in p53-null MEFs increased the secretion of the oncogenic chemokines stromal cell-derived factor-1 (SDF-1)/CXCL12 and CXCL1, proposing a novel mechanism by which stromal mut-p53 may promote tumor growth [321, 340]. Tumor angiogenesis is a hallmark of cancer and is critical for tumor growth, proliferation, and metastasis. It is characterized by the formation of abnormal, tortuous, and poorly organized vessels with altered permeability within the tumor tissue [314, 341, 342]. The ability to promote tumor angiogenesis, stimulating the release of pro-angiogenic soluble mediators in the tumor stroma, has also been ascribed to mut-p53 proteins [302, 321]. Fontemaggi *et al.* [277] established that the effect of mut-p53 proteins on tumor angiogenesis is opposite to that of WT p53; mut-p53 directs the transcriptional activity of E2F1 when bound to the regulatory region of ID4, a member of the ID family of proteins with a role in neovascularization [277, 343]. They found that ID4 participates in posttranscriptional stabilization of the pro-angiogenic cytokines IL-8 and GRO-α, resulting in increased angiogenic potential of cancer cells [277, 343–345]. Moreover, numerous studies have addressed the role of mut-p53 proteins in the induction of the pro-angiogenic extracellular mediator VEGF to sustain angiogenesis and cancer growth; in this regard, a significant direct correlation between mut-p53 protein expression and VEGF expression has been observed in human breast cancer [346]. Moreover, it has been reported that exogenous expression of mut-p53 proteins in NIH3T3 fibroblasts can induce VEGF production [276]. Intriguingly, Narendran *et al.* [347] showed that expression of mut-p53 proteins in bone marrow stromal cells can increase both the expression and secretion of VEGF in the tumor stroma, which supports the growth of leukemic cells through both paracrine and autocrine mechanisms.

In addition, a glycoprotein enzyme called prostate-specific antigen (PSA), which belongs to the kinin-releasing enzyme family, has been found in serum, and pancreatic agglutinin-like proteins are commonly used as serological or tissue tumor markers for the early detection of prostate cancer. PSA is a glycoprotein enzyme that belongs to the family of kallikreins, chymotrypsin-like proteins commonly used as serological or tissue tumor markers for the early detection of prostate cancer [348]. Downing *et al.* [349] reported a strong correlation between the expression of mut-p53 proteins and increased PSA serum levels, which are generally associated with more aggressive cancer features in mouse models of prostate cancer. Moreover, PSA transcription has been demonstrated to be strongly repressed by WT p53, while in contrast, mut-p53 proteins have been shown to stimulate the gene transcription and secretion of the biomarker PSA in cancer cells [350]. In that study, various p53 mutants (F134L, M237L, and R273H) were introduced into LNCaP prostate cancer cells to inactivate endogenous WT p53. Exogenous expression of all mut-p53 proteins in cancer cells has been observed to be strongly related to enhanced levels of PSA mRNA as well as to increased PSA protein secretion and activity compared with those in the WT p53-expressing cancer cells used as controls. Furthermore, increased PSA serum levels have been found in mice bearing tumors derived from mut-p53-expressing cells compared with those in mice implanted with WT p53-expressing control cells. These in vitro and in vivo results strongly suggest that the PSA level may be a tissue-specific indicator of WT or mut-p53 expression in prostate cancer [349]. Other proteases belonging to the kallikrein superfamily of serine proteases (for instance, kallikrein-6) have been observed to be upregulated in the secretome of some cancer cells lacking functional WT p53 [351]. These results

should prompt further studies devoted to the discovery of additional mut-p53-related serum biomarkers to provide novel diagnostic, prognostic and therapeutic tools for use in cancer patients harboring *TP53* gene mutations.

5.2 | Microbiome

In recent years, a growing body of research evidence has shown that the microbiota is strongly associated with cancer and even plays a key role in cancer development and metastasis. For example, it has been shown that most solid tumors contain bacteria, which are mostly "intracellular bacteria" present in cancer cells [352]. These bacteria may be tumor-specific, with different types of bacteria found in different types of tumors. In a recent study, it has been shown for the first time that a variety of unique "intracellular bacteria" present in breast cancer tissues play a key role in tumor metastasis and colonization [353], which is a major breakthrough in the traditional theory of tumor metastasis. In addition, another study demonstrated for the first time that a variety of unique "intracellular bacteria" present in breast cancer tissues play a key role in tumor metastasis and colonization, which is also a major breakthrough in the traditional theory of tumor metastasis [354]. In addition to bacteria, another group of microbial fungi are also prevalent in different tumors, and they are closely associated with tumor metastasis and reduced survival of cancer patients [355]. Although the gut microbiota has been at the forefront of research, a number of recent studies have shown that a variety of tumors coexist with the microbiota, and with studies confirming the prevalence of fungi, similar to the gut flora, in tumor tissues of 35 different cancer types, there is also a growing recognition that the polymorphic microbiome, as a hallmark of cancer, has a profound impact on tumor progression and response to anticancer therapies [354, 356]. Whereas p53 is likewise closely linked to the microbiota, a growing body of evidence emphasizes the interaction between the microbiome and *TP53* in human cancer. For example, in lung cancer, results from a comprehensive study showed microbiome-gene and microbiome-exposure interactions in squamous cell carcinoma lung cancer tissues [357]. In addition, *TP53* mutations are more prevalent in smokers, and *TP53*-mutant tumors are more abundant in *Massilia* and *Acidovorax*, which are also capable of affecting DNA damage recombination and repair pathways through degradation of polycyclic aromatic hydrocarbons (PAH) and lead to genetic alterations that occur in tumor cells and promote cancer progression [358]. In addition, some reports suggest that microbiota impair p53 tumor suppressor activity through mRNA instability in cancer pathophysiology. For example, some researchers have found that *Enterobacteriaceae* alleviate the selective pressure for p53 cancer-causing mutations and shape the genomic evolution of cancer through (Toll-like receptor 4) TLR4 repression of p53 [359]. In colorectal cancer, mut-p53 were found to have contrasting effects in different segments of the gut: in the distal gut, mut-p53 had the expected oncogenic effect; however, in the proximal gut and in tumor organoids, it had a pronounced tumor-suppressive effect [360]. It has been shown that p53 mutants, such as R270H and R175H, play a tumor-suppressive role in the upper gastrointestinal (GI) tract by inhibiting the activation of Wnt/β-catenin signaling [361]. In the distal intestine (colon), where gut microbes are present in a higher density, gallic acid released from bacteria appears to switch the activity of p53 mutants to oncogenic, abrogating their capability of antagonizing Wnt signaling [360].

Additionally, *Heliobacter pylori* (*H. pylori*) suppresses homologous recombination (HR), an error-free DNA damage repair pathway, while promoting non-homologous end-joining (NHEJ), an error-prone pathway, both of which are for DSBs [362]. Increasing evidence highlights that *H. pylori* can induce the degradation of p53 to interfere with the DDR process [363]. Specifically, *H. pylori*-secreted cytotoxin-associated gene A (CagA) interacts with apoptosis-stimulating protein of p53 (ASPP2), a protein activating p53 following DNA damage and consequently triggering apoptosis, and relocates it to an area near the plasma membrane, which confines p53 to the cytoplasm and consequently results in the MDM2-mediated proteasome-involved degradation of p53 [364]. More importantly, the degradation of p53 would increase the resistance of infected cells to apoptosis, thereby enhancing the colonization of *H. pylori* and predisposing these epithelial cells to cancerous transformation [364]. On the other hand, *H. pylori* also is a major risk factor for gastric cancer. Specifically, Helicobacter pylori-mediated dysregulation of upstream transcription factor 1 (USF1) impairs p53 protein stability and DNA damage response, leading to genetic instability [363]. Apart from *H. pylori*, epidermal cell-derived *Salmonella enterica* also impairs DNA damage and induces genetics/epigenetics alteration. type III secretion system (T3SS) of *Salmonella enterica* can bind the effector protein AvrA and cyclomodulin-like protein typhoid toxin, promoting tumorigenesis genetically and epigenetically, through genotoxin-mediated mutagenesis [365]. Specifically, AvrA promotes cell proliferation and differentiation and inhibits cell cycle arrest via the JAK/STAT, Wnt/ β-catenin or acetyltransferase-targeted p53 pathway, collectively resulting in tumorigenesis [366, 367]. To sum up, cancer-promoting bacteria may participate in the process of oncogenesis through a variety of different molecular pathways, and several main mechanisms are summarized here (Figure 8).

6 | THERAPY RESISTANCE MEDIATED BY ALTERED P53

6.1 | Chemotherapy

Resistance to anticancer drugs is the major obstacle to curative cancer therapeutics. Mutations in p53 and p53 variants play important roles in cellular sensitivity and resistance to antitumor drugs, such as cisplatin, 5-Fluorouracil (5-FU), temozolomide (TMZ), Dox, paclitaxel (PTX), etoposide and carfilzomib. Induction of apoptosis is one of the most important functions of p53, and disruption of this function promotes tumor chemoresistance [201]. p53-based drug resistance is strongly associated with the chemical properties of the drug, the biological function or pathway of the drug disrupted, the cellular target of the drug, the genomic instability of the tumor, and the degree of tumor differentiation. Although substantial advances have recently been made in the treatment of cancer, chemotherapeutic drugs remain a primary component of most current cancer therapies. However, drug resistance, and often multidrug resistance, is the primary reason for the failure of clinical chemotherapy. In addition, chemotherapy induces numerous cellular responses, such as apoptosis, autophagy, and senescence.

For example, WT p53 can induce apoptosis through mitochondrial and Fas-mediated apoptotic pathways [154, 368]. As shown in Figure 9, WT p53 induces oligomerization of Bax, bakuchiol (BAK), and voltage-dependent anion-selective channel (VDAC), increases the permeability of the outer mitochondrial membrane, and promotes the release of cytochrome C [369]. Chemotherapeutic agents such as 5-FU and oxaliplatin sensitize colorectal cancer cells carrying WT p53 to FAS-mediated apoptosis [370]. In contrast, the p53 R175H, L194F, R249S, and R280K mutants lose the ability to activate the formation of BAX/BAK lipid membrane pores and alter the VDAC multimerization state, which inhibits apoptosis in cancer cells [368]. In osteosarcoma, the p53 R273H mutant reduces the expression of pro-caspase-3, resulting in failure of chemotherapeutic agents such as methotrexate and Dox to induce apoptosis [371]. In colon cancer, mut-p53 does not bind to the PUMA promoter to activate its transcription, facilitating apoptosis evasion by tumor cells and reducing sensitivity to 5-FU [372]. Furthermore, in tumor cells lacking functional p53, various chemotherapeutic agents can cause apoptosis by inducing the expression of p73 [373]. However, mut-p53 can inactivate p73 in colon cancer, and downregulation of mut-p53 enhances chemosensitivity [373]. In colorectal cancer, mut-p53 activates ephrin-B2 (EFNB2) in response to DNA damage, while silencing EFNB2 increases the sensitivity of cancer cells to 5-FU [292]. Additionally, studies have shown that high expression of multidrug resistance gene 1 (MDR1) is significantly correlated with chemoresistance in different cancers. For instance, in colon cancer and osteosarcoma, mut-p53 specifically upregulates MDR1 expression by interacting with Ets-1, which leads to chemoresistance [291]. In colorectal cancer, 5-FU promotes the expression of p53 [374]. However, in contrast to WT p53, mut-p53 cannot inhibit leucine-rich pentatricopeptide repeat-containing protein (LRPPRC) expression after DNA damage, resulting in an increase in MDR1 transcription, which finally leads to chemoresistance [375]. Therefore, these results indicate that p53, whether present or mutated, plays a crucial role in regulating chemotherapy resistance of tumor cells (Figure 9).

6.2 | RT

6.2.1 | p53 turns up the heat for RT sensitization

As a master regulator of cellular homeostasis, p53 has been shown to be involved in the control of DNA damage-induced apoptosis. Loss or malfunction of this p53-mediated apoptotic pathway has been proposed as one mechanism by which tumors become resistant to chemotherapy or radiation. Systemic p53-based cancer therapeutics result in efficient expression of functional WT p53, sensitizing tumors to chemotherapy and RT. This is a novel strategy combining current molecular medicine approaches with conventional chemotherapy and RT for cancer treatment. Tumor cells adapt to permit uncontrolled growth and survival by developing oncogene or non-oncogene "addiction", which renders them highly dynamic and evasive in their responses to treatment (Figure 10).

Stressors that activate p53 do not always result in the same outcome. For example, although different doses of a single DNA-damaging agent, such as the chemotherapeutic drug Dox, can activate p53, the outcome is completely variable. p53 activation by low-dose Dox results in cell survival, whereas higher doses produce more widespread cell death. Similarly, cells have evolved elaborate mechanisms (checkpoints) to monitor genomic integrity to ensure the high-fidelity transmission of genetic information [376]. Cells harboring defects in checkpoint pathways respond inappropriately to DNA damage, which in turn may increase the rate of cancer development [377]. IR leads to DSBs, which activate DNA damage checkpoints to initiate signaling, ultimately leading to a binary decision between cell death and cell survival [378–380]. In addition, exposure to radiation may contribute to blockade of the G1/S transition, resulting in S-phase arrest. In theory, G1/S

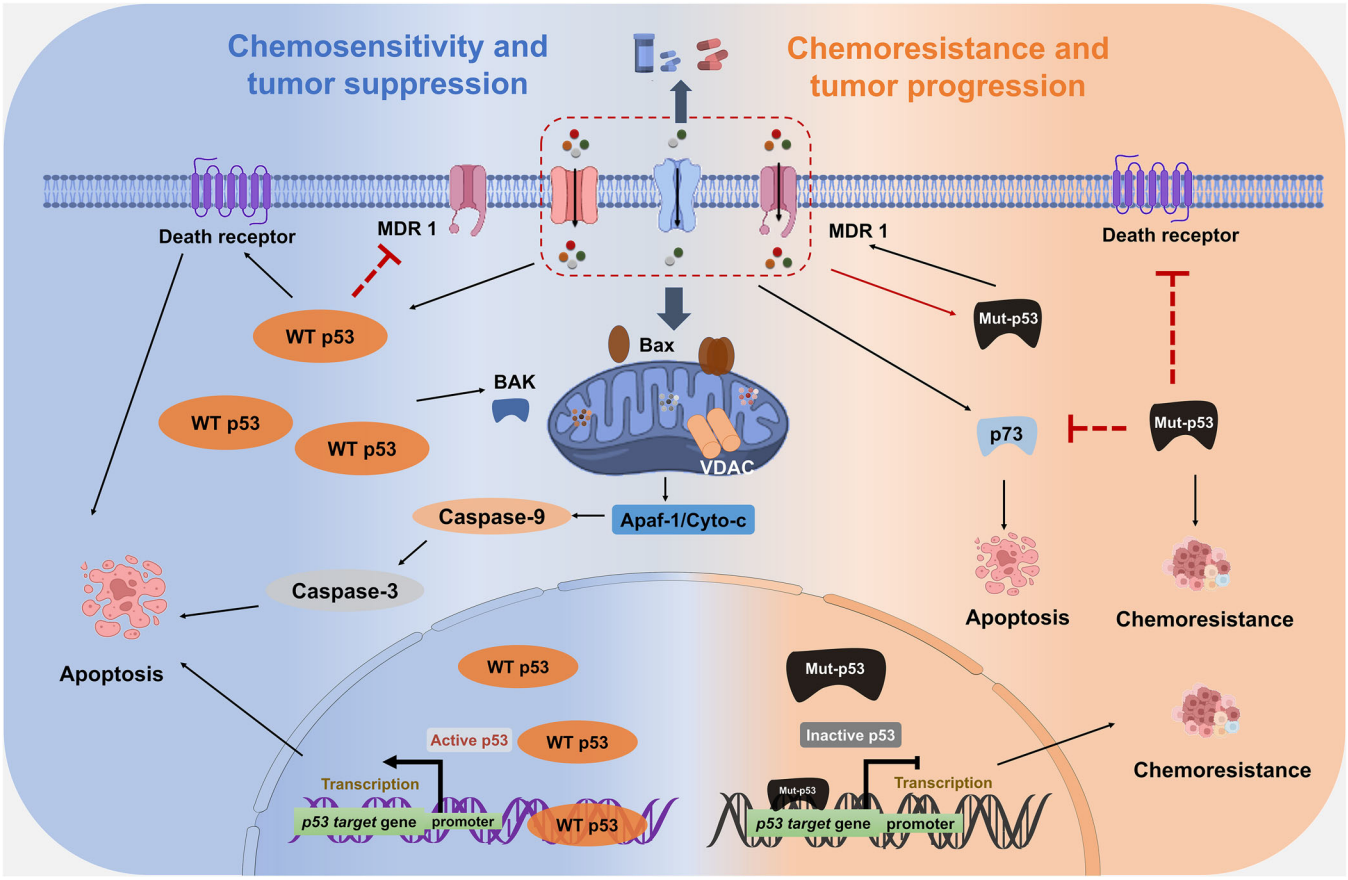

FIGURE 9 Schematic representation of the mechanism of mut-p53 in the response to chemotherapy. The expression of mut-p53 is positively correlated with increased resistance to chemotherapy in different cancers. Data were retrieved from and based on reference [201]. MDR1, multiple drug resistance 1; VDAC, voltage-dependent anion channel; WT, wild type; mut-p53, mutant p53; BAK, bcl2 antagonist/killer 1; Bax, bcl-2-associated X protein

arrest allows cells exposed to radiation more time to perform DNA damage repair [381–383]. For example, several groups have reported the increased sensitivity of mut-p53 tumor cells to chemotherapy [372] and RT [384]. A series of elegant studies demonstrated that the p38 MAP kinase-MAPKAP kinase-2 (MK2) signaling node complements the well-established ATM-Chk2 and ATR-Chk1 nodes that converge on the cell cycle regulator Cdc25 during the DDR [385, 386]. The mechanism by which p38-MK2 regulates the DDR in a mut-p53-dependent manner was shown to act through the G1/S and G2/M checkpoints, resulting in synthetic lethality [387].

In addition, previous studies have indicated that p53, a crucial TF that has also been recognized as a vital checkpoint protein, functions mainly through transcriptional control of target genes that regulate cell fate and lead to diverse responses to radiation in mammalian cells [388, 389], especially by monitoring G1 and G2/M checkpoints [390]. G1 arrest is associated with the p53 status. G1 arrest is related to p53 status. Loss of G1/S arrest and synchronized mitotic selection after radiation are demonstrated in cancer cells expressing WT p53 [391]. Some researchers have found that p53 is phosphorylated and regulated by a series of proteins [392]. First, BRCA1 is phosphorylated at 2 sites, S1423 and S1524, based on regulation by ATM/ATR. Then, ATM/ATR are activated by phosphorylation of BRCA1 to phosphorylate p53 at S15. Consequently, phosphorylated p53 functions in monitoring G1/S arrest by inducing p21, which is reported to be a CDK inhibitor. Compare the differences in the G1 phase population of colon cancer cells with $p53^{+/+}$ and $p53^{-/-}$ genotypes after irradiation. The results showed that in $p53^{-/-}$ cancer cells, the G1 population was significantly reduced at the same time. [393]. It has also been determined that Krüppel-like factor 4 (KLF4) mediates p53 activation to control G1/S arrest following irradiation, indicating that the regulatory role of p53 in the radiation response in cancer cells is complex and that p53 is a key factor in the process [393]. Thus, recovery or activation of p53 could be a strategy for overcoming the effects of radiation. On the other hand, recent research has suggested that ATM is activated to phosphorylate p53 to facilitate its binding to f-box and WD repeat

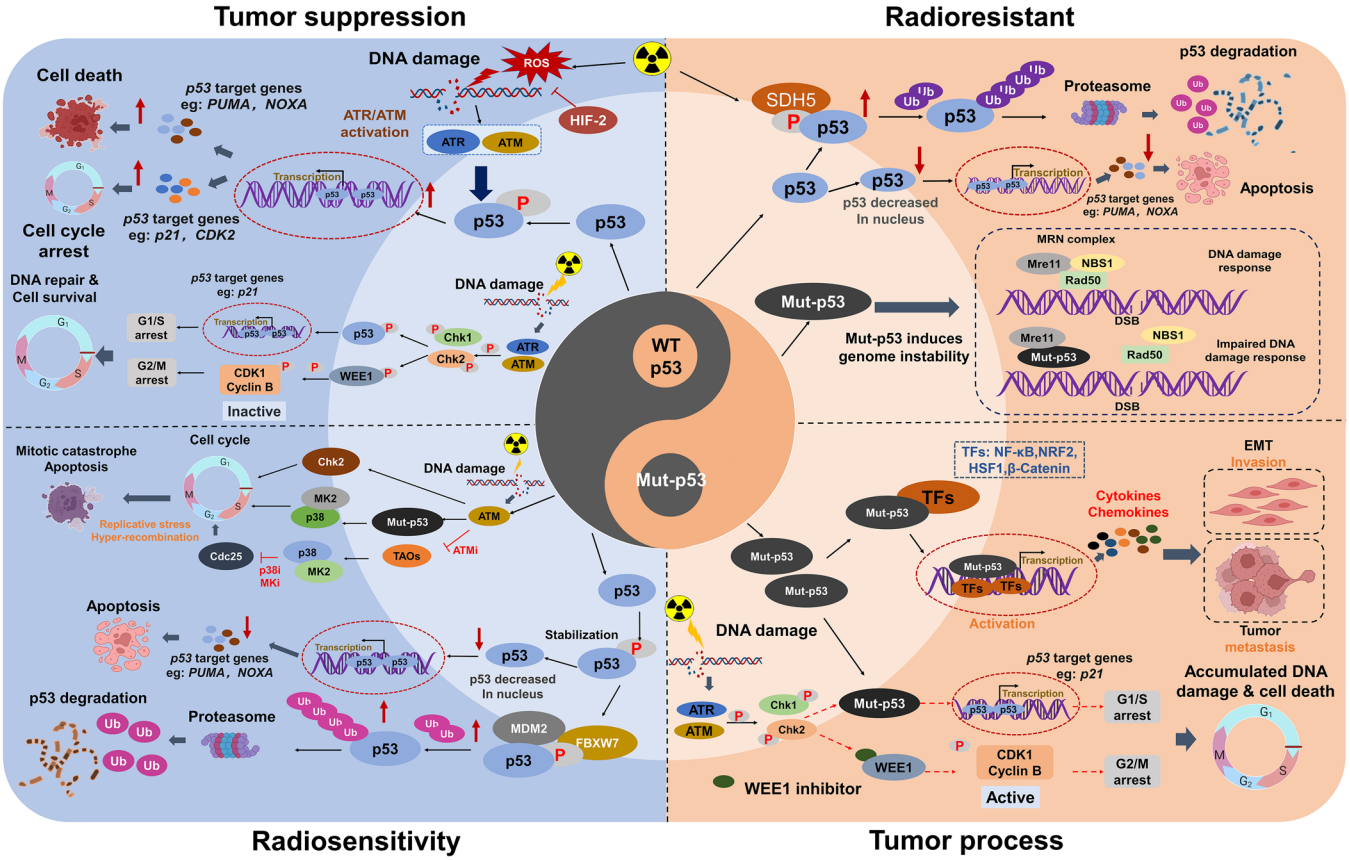

FIGURE 10 Schematic representation of the multiple mechanisms that regulate p53 activity and cell fate in response to RT. Mut-p53 can regulate the response to RT through various mechanisms. In most cases, expression of mut-p53 leads to radioresistance. However, in certain contexts, mut-p53 expression can have no effect on or even promote radiosensitivity. Data were retrieved from and based on reference [20, 191, 398]. EMT, epithelial-to-mesenchymal transition; ATM, ataxia-telangiectasia-mutated kinase; ROS, reactive oxygen species; TF, Transcription factor; ATR, ataxia-telangiectasia and Rad3 related; RT, radiotherapy; mut-p53, mutant p53; PUMA, p53 up-regulated modulator of apoptosis; NOXA, phorbol-12-myristate-13-acetate; CDK1, cyclin-dependent kinase 1; CDK2, cyclin-dependent kinase 1; CDK2, cyclin-dependent kinase 2; WEE1, Wee1-like protein kinase; HIF-2, hypoxia inducible factor-2; SDH-5, succinate dehydrogenase-5; Ub, ubiquitin; DSB, DNA double-strand break; MRN, MRE11-RAD50-NBS1; NBS1, Nijmegen breakage syndrome 1; NRF2, nuclear factor erythroid 2-related factor 2; HSF1, heat shock factor 1; mdm2, murine double minute 2; FBXW7, f-box and WD repeat domain containing 7

domain containing 7 (FBXW7), leading to p53 ubiquitination and proteasomal degradation. Biologically, FBXW7 inactivation sensitizes cancer cells to radiation and etoposide (VP-16) by stabilizing p53 to induce cell cycle arrest and apoptosis [394].

In addition, post-irradiation, ATM phosphorylates both NBS1 (nijmegen breakage syndrome 1) and Chk2, leading to S-phase checkpoint activation. Ultimately, the distinct steps of DNA replication are suppressed [395]. Regulation of the S-phase checkpoint is complex and involves multiple pathways; thus, determining whether cancer cells are dependent on one, both, or neither of these intra-S-phase checkpoints in response to radiation is necessary. G2/M arrest prevents cells from entering the M (mitosis) phase when DSBs are present [396]. Although several questions remain to be addressed, current evidence suggests that p53-mediated regulation of the RT response in tumors shows a Yin-Yang balance. The "dark side" (Yin), which includes inhibition of cancer cell development and a desirable RT response, comprises the effects of p53 on cancer cells themselves and its functions as a cellular "guardian angel". This side is associated with DNA damage signaling, as well as coordinating DNA DSBs for recognition of the target cell as a response stressor. These features provide a distinct opportunity to combine p53-targeted therapies with current radiotherapies to develop more effective cancer treatments (Figure 10).

6.2.2 | Mut-p53 augments radio-resistance

The p53 mutational spectrum differs among cancers of the colon, lung, esophagus, breast, liver, brain, reticuloendothelial tissues, and hemopoietic tissues [397]. p53

mutations increase resistance to IR. Mouse and human tumors of diverse origins frequently harbor somatically acquired mutations or rearrangements of the *p53* gene or loss of one or both copies of the gene. Although the WT p53 protein is believed to function as a tumor suppressor gene, the mechanism by which p53 mutations lead to neoplastic development is unclear [398]. WT p53 has been postulated to play a role in DNA repair, suggesting that the expression of mutant forms of p53 might alter cellular resistance to the DNA damage caused by γ-radiation [399]. Moreover, p53 is thought to function as a cell cycle checkpoint after irradiation, also suggesting that mut-p53 might change the cell proliferation response to radiation. Transgenic mice expressing 1 or 2 mutant alleles of p53 were used to test this prediction. Some results showed that expression of both mutant variants of the mouse p53 gene significantly increased the resistance of diverse hematopoietic cell lineages to γ-radiation. These observations provide direct evidence that p53 mutations affect the cellular response to DNA damage, either by enhancing DNA repair processes or possibly by increasing cellular tolerance to DNA damage [399, 400]. The association of p53 mutations with increased radio-resistance suggests possible mechanisms through which alterations in the p53 gene might lead to oncogenic transformation [401].

In diffuse intrinsic pontine gliomas, mutations in p53 are a major driver of increased radiation resistance, with mut-p53-carrying patients less responsive to irradiation and relapsing earlier after RT with a worse prognosis [402]. O'Connor *et al.* [403] studied the response to radiation based on the p53 status in 60 different cancer cell lines. In contrast to cells carrying WT p53, most tumor cells carrying mut-p53 did not exhibit induction of protein p21 (CIP1/WAF1), growth Arrest and DNA Damage-inducible 45 (GADD45), and MDM2 mRNA expression or G1 arrest after γ-irradiation, resulting in radio-resistance [403]. In bladder cancer, IR can induce tumor cells carrying WT p53 to undergo G1 arrest and apoptosis, resulting in increased radio-sensitivity. In contrast, this phenomenon was not significantly observed in tumor cells carrying mut-p53 [404] (Figure 10). Some studies have demonstrated that mut-p53 loses the ability to induce G1 arrest after γ-irradiation [405]. In GB, clonogenic survival assays showed that U87 cells carrying WT p53 and T98 cells carrying mut-p53 exhibited essentially identical sensitivity to fractionated RT. However, cells carrying WT p53 exhibited accelerated senescence in response to IR [406]. In ovarian cancer, cells carrying WT p53 are very sensitive to irradiation, which leads to p53 accumulation after irradiation, whereas cells carrying mut-p53 show varying degrees of radio-resistance, and p53 accumulation does not occur after irradiation [407]. In head and neck cancer [408], hepatocellular carcinoma [409], cervical cancer [410], and endometrial cancer [411], cells carrying mut-p53 are also more resistant to radiation. Furthermore, in transgenic mice carrying mut-p53, the resistance of various hematopoietic cell lineages to γ-irradiation was found to be increased, and overexpression of the p53 R193P or A135V mutants increased the radio-resistance of mouse hematopoietic cells, as determined by the survival rate of 45%-57% [412]. Notably, the relationship between mut-p53 and radiosensitivity is controversial, as some studies suggested that mut-p53 may affect or increase radiosensitivity. [413]. For instance, Kawashima *et al.* [413] introduced the p53 R273H mutant into immortalized human fibroblasts and found that cells carrying the p53 R273H mutant had higher radio-sensitivity than cells not expressing p53 after X-ray irradiation. Rat lung embryonic epithelial cells carrying mut-p53 display significantly lower survival after γ-irradiation at doses of 2 to 12 Gy than those carrying WT p53, suggesting that mutations in p53 increase sensitivity to IR [414]. Interestingly, cells expressing p53 mutants with mutations at different sites are differentially sensitive to RT [415]. For example, osteosarcoma cell lines with p53 mutations at codons 175, 244, 245, 273, and 282 were found to be radio-resistant after γ-irradiation treatment. In addition, mutations in codons 123, 195, and 238 boost radio-sensitivity compared to that in cells harboring WT p53, while mutations at codons 130, 143, 157, 168, 277, 280, and 286 lessen radio-sensitivity [415]. Radio-sensitivity is also affected by phosphorylation. Lung cancer cells harboring the p53 S15A and S46A mutations are radiosensitive, whereas cells with the p53 S15D, S20A, and S20D mutations are less radio-sensitive [416]. Furthermore, Tada *et al.* [417] used a sensitive yeast functional assay to determine the status of p53 in a trial of 36 patients with GBM treated with RT and revealed that patients with mut-p53 had a longer regrowth-free period after treatment. However, WT p53 effectively abrogates IR-induced autophagy and activates apoptosis to regulate radio-sensitivity in lung cancer, while the p53 R175H mutant has no effect on radio-sensitivity [418]. Thus, further research is needed to determine the link between mut-p53 and the response to RT, which is of great clinical significance for the treatment of patients.

6.3 | Immunotherapy

Cancer immunotherapy regimens have recently generated great enthusiasm, owing to their unprecedented success in several types of cancer. The renaissance of cancer immunotherapy is also kindling renewed interest in p53-based strategies, mainly those aimed at increasing the ability of the immune system to recognize and eradicate cancer cells that harbor deregulated p53 [206]. The expectation that such strategies might be effective is based

largely on the observation that cancer cells that harbor *TP53* missense mutations often overexpress p53 and might therefore be expected to display greater amounts of p53-derived peptides on their surfaces through major histocompatibility complex (MHC) molecules [14].

One major caveat, however, is that although the abundance of mut-p53 proteins in cancer cells is driven partially by increased transcription of p53 mRNA and subsequent protein translation, it is due mainly to the inefficient degradation of mut-p53 by the ubiquitin-proteasome system [419]. Tumor cells elicit immunogenic responses due to "hotspot" mut-p53 epitopes (such as p53-derived peptides as a neoantigens) produced via proteasomal degradation of intracellular protein and presented by MHC. However, studies performed over the past two decades raise hope that p53-based immunotherapy may eventually gain clinical relevance (Figure 11).

Broadly speaking, overexpression of missense mut-p53 proteins in cancer cells is expected to increase the presentation of various peptides derived from regions throughout the p53 protein. Although at least some of these peptides might be shared with WT p53, the selectivity of the immune system for cancer cells depends on the very low expression level of p53 in normal cells. The feasibility of this approach is supported by the observation that the T cell response to p53 expression is not restricted by natural self-tolerance [420]. However, the assumption that healthy cells will not be affected is risky. Indeed, differentiated cells may express extremely low amounts of p53 mRNA and hence synthesize hardly any p53 protein, but this assumption may not hold for rapidly proliferating normal progenitor cells, in which *TP53* mRNA expression is more substantial [421].

6.3.1 | p53-based vaccines

Vaccination attempts aimed at enhancing cellular immunity against cancer cells that contain highly excessive amounts of p53 were initiated in the 1990s [422–424]. The sequences of the peptides used in those attempts were derived from regions of the WT p53 protein that are rarely mutated in cancers and thus are shared with cancer-associated mut-p53. However, selectivity for cancer cells was achieved because normal cells possess very low amounts of p53 and thus are not expected to be recognized and attacked by the immune system of the vaccinated host. Subsequently, a synthetic long peptide (SLP) vaccine comprising ten overlapping peptides from the WT p53 sequence (collectively representing amino acids 70-248), administered by 2 injections at a 3-week interval, was shown to elicit a T cell response predominated by $CD4^+$ T cells in metastatic colorectal cancer [425]. Adverse events were relatively mild: toxicity was limited to grades 1/2 and was observed mostly at the vaccination site [425]. In patients with ovarian cancer, p53 immunogenicity was potentiated by low-dose cyclophosphamide treatment before SLP vaccination [426]. However, a clinical trial failed to show a benefit of SLP vaccination over historical control approaches [426]. A modified vaccinia Ankara (MVA) vaccine encoding WT p53 (MVAp53) was also tested in early-phase clinical trials in patients with refractory GI cancer and ovarian cancer and was found to induce $CD8^+$ and $CD4^+$ T cell responses in 6 and 5, respectively, of the total of 11 responding patients [427, 428]. Importantly, patients who exhibited an immune response after p53 vaccination had significantly longer progression-free survival times than patients with no $CD8^+$ T cell expansion [427]. Further clinical trials using the MVAp53 vaccine in combination with the anti-programmed cell death protein 1 (anti-PD-1) antibody pembrolizumab are currently ongoing (NCT03113487 and NCT02432963). In a complementary approach, autologous dendritic cells (DCs) were modified to display p53 peptides via MHC class I and II molecules [429]. This DC-p53 vaccine triggered a p53-specific immune response in 16 of the 28 patients with SCLC treated [430]. Importantly, of the 21 patients who received secondary chemotherapy after p53 vaccination, 13 showed an objective clinical response [431]. Disappointingly, a phase II randomized trial of PTX (paclitaxel) following treatment with the DC-p53 vaccine or control revealed no difference in the overall response rate [432].

The success of mRNA vaccination during the coronavirus disease 2019 (COVID-19) pandemic raises new hopes for the development of a p53 mRNA vaccine. Notably, this avenue has already been explored. Remarkably, after the introduction of autologous *TP53* mRNA-transfected DCs into patients with breast cancer, 13 of 18 patients with tumors expressing high levels of p53 displayed a p53-specific interferon-γ (IFN-γ) T cell response in vitro; this was in striking contrast to the p53-specific IFN-γ T cell response in healthy donors and in patients with breast cancer with low p53 expression (1 of 10 and 2 of 18, respectively) [433]. This approach is likely to see a revival with the recent advances in methodologies.

6.3.2 | p53-based adoptive cell transfer (ACT)

ACT is one category of cancer immunotherapy and has marked clinical benefits in patients with advanced cancers, such as metastatic melanoma [434, 435]. For patients with metastatic melanoma, the response rate is ~50%, and some patients have achieved very long-term remission [435]. There are several types of ACT. One type is

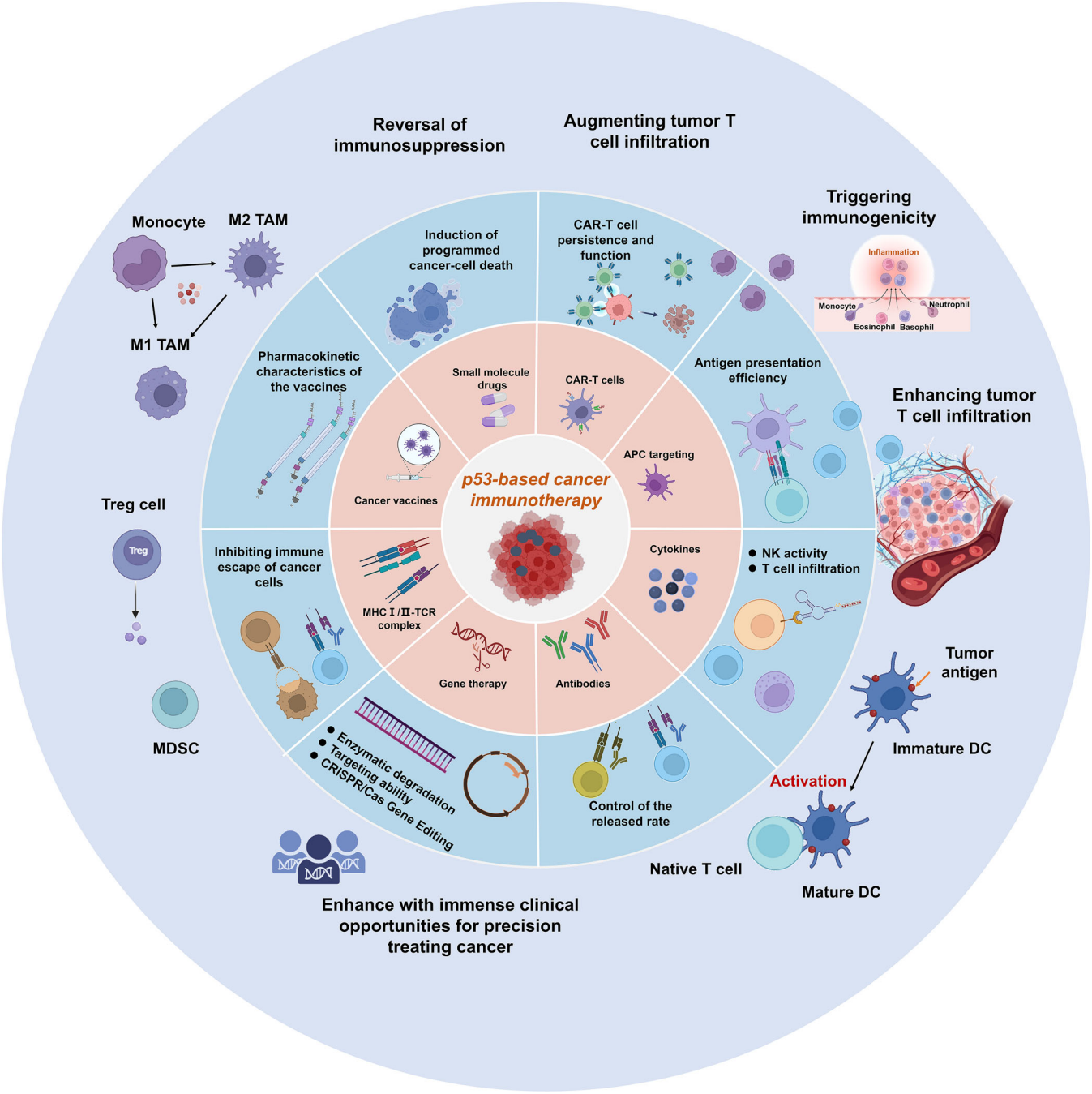

FIGURE 11 A framework for exploiting the immunogenicity of p53-based cancer immunotherapies. Tumor cells carrying mut-p53 or apoptotic bodies can be engulfed by APCs. MHC II molecules on APCs present mut-p53-derived neoantigens to $CD4^+$ T cells, which help B cells to produce antibodies against the neoantigens. Most tumor cells express MHC I molecules, which self-present mut-p53-derived neoantigens. $CD8^+$ T cells are activated through interactions between MHC I molecules and TCRs. Activated $CD8^+$ T cells (cytotoxic T cells) can attack tumor cells. TILs, comprising mostly $CD8^+$ T cells and NK cells, can be isolated from tumors, expanded to a large number *ex vivo*, and infused back into the same patient to attack the tumors. TCRs specific for mut-p53-neoantigens can be cloned and packaged into viral particles to generate either TCR-T cells or CAR-T cells, which are infused back into the same patient. Cancer cells carrying mut-p53 can be targeted with immunotherapy using mut-p53-specific TILs or TCR-T cells. At the protein level, the DNA-binding and transcriptional functions of mut-p53 can be restored using small molecule reactivators that stabilize the protein in its active biological conformation. At the gene level, *TP53* mutations can be repaired using CRISPR/Cas9 gene editing approaches such as HDR, base editing and prime editing. Data were retrieved from and based on reference [14, 206, 282]. HDR, homology-directed repair; HLA, human leukocyte antigen; PBL, peripheral blood lymphocyte; TCR, T cell receptor; TIL, tumor-infiltrating lymphocyte; APC, antigen-presenting cell; mut-p53, mutant p53; MHC, major histocompatibility complex; NK, natural killer; CAR-T, chimeric antigen receptor T; TAM, tyro3, axl, and mertk; Treg, regulatory T cells; MDSC, myeloid-derived suppressor cells; DC, dendritic cells; APC, activated protein C

called tumor-infiltrating lymphocytes (TIL)-ACT; in this method, T cells are isolated from cancer patients, propagated in large quantities *ex vivo*, and then infused back into the same patients to attack the tumor (Figure 11). Another type of ACT is T cell receptor (TCR)-ACT. In TCR-ACT, TCRs are cloned from T cells that recognize a small peptide released from tumor cells called tumor antigen. The cloned TCRs are packaged into a retrovirus, lentivirus, or Sleeping Beauty transposon system (a baculovirus system), which are subsequently used to transduce T cells. These engineered T cells (TCR-T cells) can then specifically target tumor cells and mediate tumor regression after being reinfused into the patient. The third type of ACT is chimeric antigen receptor-T (CAR-T) cell therapy. CAR-T cells are different from TCR-T cells in that the TCR in CAR-T cells is engineered to contain both antigen binding and T cell stimulation modules (and is thus chimeric). Three CAR-T cell therapies have received US FDA approval for treating B cell precursor acute lymphoblastic leukemia, relapsed or refractory large B cell lymphoma, and relapsed or refractory mantle cell lymphoma.

A critical step in generating effective TCR-T or CAR-T cells is to clone/engineer a TCR that is highly specific for tumor neoantigens. Neoantigens are antigens derived from mutated proteins in tumor cells. Due to their high expression levels in tumors, p53 mutants are good candidates for neoantigen production. In 1979, Linzer *et al.* [25] found that sera from mice with transformed tumors had antibodies against endogenous p53. This was the first report showing that the p53 protein is immunogenic and can activate the $CD4^+$ T (T helper) cell response. Later studies showed that both human and murine WT p53 and certain p53 mutants exhibit immunogenicity and can activate $CD8^+$ T cells (cytotoxic T cells) [436–438], although these studies were performed under non-endogenous conditions. Whether endogenous mut-p53 in human tumors can activate T cell responses and whether peptides containing p53 mutations are immunogenic remain unclear.

A recent study investigating the immunogenicity of p53 mutants in 140 patients with different tumor types found that endogenous p53 mutants can trigger $CD4^+$ (helper) and $CD8^+$ (cytotoxic) T cell responses [439]. In addition, isolated TILs and TCR-engineered T cells recognized cancer cell lines that endogenously expressed p53 mutants. Although this study did not show whether these TILs and TCR-engineered T cells had therapeutic benefits in tumor regression, it demonstrated that endogenous p53 mutants in human tumor cells are immunogenic and marked the first step for mut-p53-based ACT approaches. Notably, not every peptide containing a *TP53* mutation is immunogenic, probably due to the sequence requirement for neoantigens. However, peptides containing the hotspot mutations R175H, Y220C, G245S, R248Q, R248W, and R282 were shown to activate T cell responses, albeit with a wide range of frequencies [439].

Going forward, it is conceivable that a collection of TCRs could be cloned and used to recognize neoantigens derived from certain immunogenic *TP53* mutants. This collection of TCRs could then be either used in TCR-ACT or engineered for use in autologous or allogeneic CAR-T cell therapy. There are several phase I clinical trials evaluating the safety and efficacy (response rate) of anti-p53 TCR-engineered lymphocytes in metastatic tumors (for example, NCT00393029 and NCT00496860). However, whether these engineered lymphocytes have the clinical benefit of inhibiting tumor growth is unclear [440].

6.3.3 | p53-based specific antibodies

Other p53-based immunotherapeutic approaches are also emerging. T cell receptor mimic (TCR-m) antibodies, also called TCR-like antibodies, are a potential strategy to target intracellular proteins. These antibodies, usually generated by phage display library screening or hybridoma screening, recognize epitopes presented by MHC class I molecules on the cell surface, similar to the process by which such epitopes are recognized by T cells via their TCRs, enabling the recognition of peptides derived from intracellular proteins. Accordingly, researchers developed a novel TCR-m antibody that recognized a p53-derived epitope presented selectively by MHC class I molecules on cancer cells but not on normal peripheral blood mononuclear cells [441]. Importantly, this p53 TCR-m antibody elicited tumor regression in mice carrying breast cancer xenografts. Similarly, a p53-specific TCR-like antibody designated P1C1TM was generated. Although designed on the basis of a WT p53 peptide, P1C1TM elicited selective antibody-dependent cellular cytotoxicity toward cancer cells that harbored several different p53 mutations, presumably owing to their high p53 protein abundance. As an additional therapeutic advantage, P1C1TM also facilitated drug delivery into p53-mutated cancer cells via antibody-drug conjugates [442].

An alternative approach relies on the idea that peptides that contain the mutated amino acid of a p53 missense mutant act as neoantigens when presented by MHC molecules. The extensive diversity of *TP53* missense mutations in human cancers indicates a wealth of potential neoantigens. Immune responses elicited against such neoantigens are specific to cancer cells harboring these particular mutations and do not endanger rapidly proliferating normal cells. The attractiveness of mut-p53-derived peptides as targets for cancer-specific immunotherapy has long been noted [443]. Recent work has confirmed that mut-p53 proteins may give rise to neoantigens that are

presented by MHC molecules and activate a mut-p53-specific immune response [439, 444, 445]. Notably, the peripheral blood of cancer patients who mounted a TIL response to mut-p53-derived neoantigens also contained mut-p53-specific reactive T cells, raising hope that such peripheral blood T cells might be used for adoptive cell therapy in patients with tumors harboring the same *TP53* mutation [446].

Bispecific antibodies are a very promising approach to cancer immunotherapy [447]. Indeed, an engineered single-chain mut-p53-based bispecific antibody recognizing a neoantigen derived from the p53 (R175H) hotspot mutant and the TCR-CD3 complex was recently generated [448]. Usually, the low density of such neoantigens on the surface of cancer cells hinders their elimination by the immune system. However, by binding with high affinity to both the mut-p53-R175H peptide-human leukocyte antigen (HLA) complex on cancer cells and the TCR-CD3 complex on T cells, this bispecific antibody overcame the paucity of neoantigen presentation and selectively redirected T cells to recognize cancer cells presenting the mutant peptide. This resulted in marked selective cytotoxicity against mut-p53-expressing cancer cells both in vitro and in vivo [448]. This approach and additional mut-p53-selective immunotherapeutic approaches are likely to gain increasing popularity in the coming years.

6.3.4 | p53-based regulation of immune response in TME

Beyond the targeted attempts to develop p53-specific immunotherapeutic modalities, recent studies have underscored a broader connection between p53 and cancer immunotherapy. Indeed, the p53 status in cancer cells can affect the immune landscape in the TME [46, 282]. Specifically, functional WT p53 in cancer cells tends to favor a cancer-suppressive TME, whereas loss of WT p53 tilts the balance toward a more cancer-supportive TME. Furthermore, some missense mut-p53 proteins, as part of their GOF activities, may further limit the ability of the immune system to attack cancer cells. For example, WT p53 can reduce the level of PD-L1 indirectly via upregulation of miR-34a [449] and induce the expression of the natural killer (NK) cell-activating ligands UL16-binding protein 1 (ULBP1) and ULBP2. These 2 transcriptional effects of WT p53, mediated by its direct binding to the corresponding target genes [450], respectively render cancer cells more susceptible to attack by cytotoxic T cells and NK cells. Moreover, through regulation of cytokine expression, WT p53 can exert antitumor effects by changing the composition of the tumor immune microenvironment (TIME) [451]. Interestingly, by the use of several MDM2 inhibitors, several studies have reported that p53 activation orchestrates a tumor-suppressive microenvironment through activation of endogenous retroviruses, leading to increased IFN-γ signaling and sensitizing the tumor to immune checkpoint inhibitors [452]. Conversely, by altering the secretion of cytokines, as well as the physical properties of the TME, hotspot p53 mutants may exert GOF effects on the TIME that go beyond the mere impact of WT p53 loss [287, 453]. Hence, the p53 status of a tumor could be important for patient management decisions related to immunotherapy.

Notably, noncancerous cells in the TME retain WT p53. Hence, drugs that boost p53 activity may also augment the non-autonomous cancer-suppressive functions of p53 in the TME, as exemplified by nutlin-3a treatment of stromal fibroblasts [321]. Similarly, enhancement of p53 activity in immune cells may contribute directly to a tumor-suppressive TIME. This phenomenon was shown by a study in which the MDM2 inhibitor APG-115 exerted antitumor effects in WT p53- and mut-p53-expressing syngeneic models of hepatoma and colon carcinoma [454]. The effects in mut-p53-expressing tumors were attributed to the ability of APG-115 to promote M1 macrophage polarization, presumably through modulation of endogenous WT p53. Notably, M1 macrophages promote a cancer-inhibitory TIME, as opposed to M2 macrophages, which are associated with a more tumor-protective TIME. In contrast, $CD4^+$ T cell activation and $CD8^+$ T cell infiltration rely on the activation of p53 in cancer cells. Reassuringly, compared to each treatment alone, the combination therapy with APG-115 and a PD-L1 inhibitor conferred enhanced antitumor immunity, but this effect was abolished in Trp53-KO mice, further underscoring the importance of p53 activation in the TME [454]. A combination of APG-115 and pembrolizumab was tested in a clinical trial (NCT03611868) in patients with metastatic melanoma and advanced-stage solid tumors and demonstrated good tolerability and preliminary indications of antitumor activity [455]. Moreover, beneficial effects of combining p53 activation with immunotherapy were also observed with gene therapy modules, including nanoparticles [456] and adenovirus-p53 [457]. Given the great interest in cancer immunotherapy, further studies on such combination treatments will most certainly continue and intensify.

Although p53 has a well-established function as the "guardian of genome integrity", it has also been implicated in an increasing number of homeostatic stress responses, including those involving aspects of innate and adaptive immunity, as described above. These studies are still at a relatively early stage, but p53 may eventually be considered a "guardian of immune integrity". Notably, accumulating evidence indicates that other tumor suppressor genes may have similar functions.

7 | TARGETING P53 FOR EFFECTIVE CANCER THERAPY

TP53 is the most frequently mutated gene in tumors, with mutations leading to not only loss of function but also GOF that promotes tumor progression and metastasis. Because of the tumor-specific status of the mut-p53 protein and the differences between normal and tumor cells, p53 is a promising target for cancer therapy. Potential therapeutic strategies include (1) approaches to activate WT p53, (2) approaches to reactive mut-p53, and (3) approaches to eradicate cells with mut-p53. However, there are very few drugs targeting p53 in phase I to phase III clinical trials (Figure 12, Table 1).

7.1 | Approaches to activate WT p53

7.1.1 | MDM2 and MDMX inhibitors

MDM2 and MDMX are major negative regulators of p53. MDM2 or MDMX deletion in mice causes early embryonic

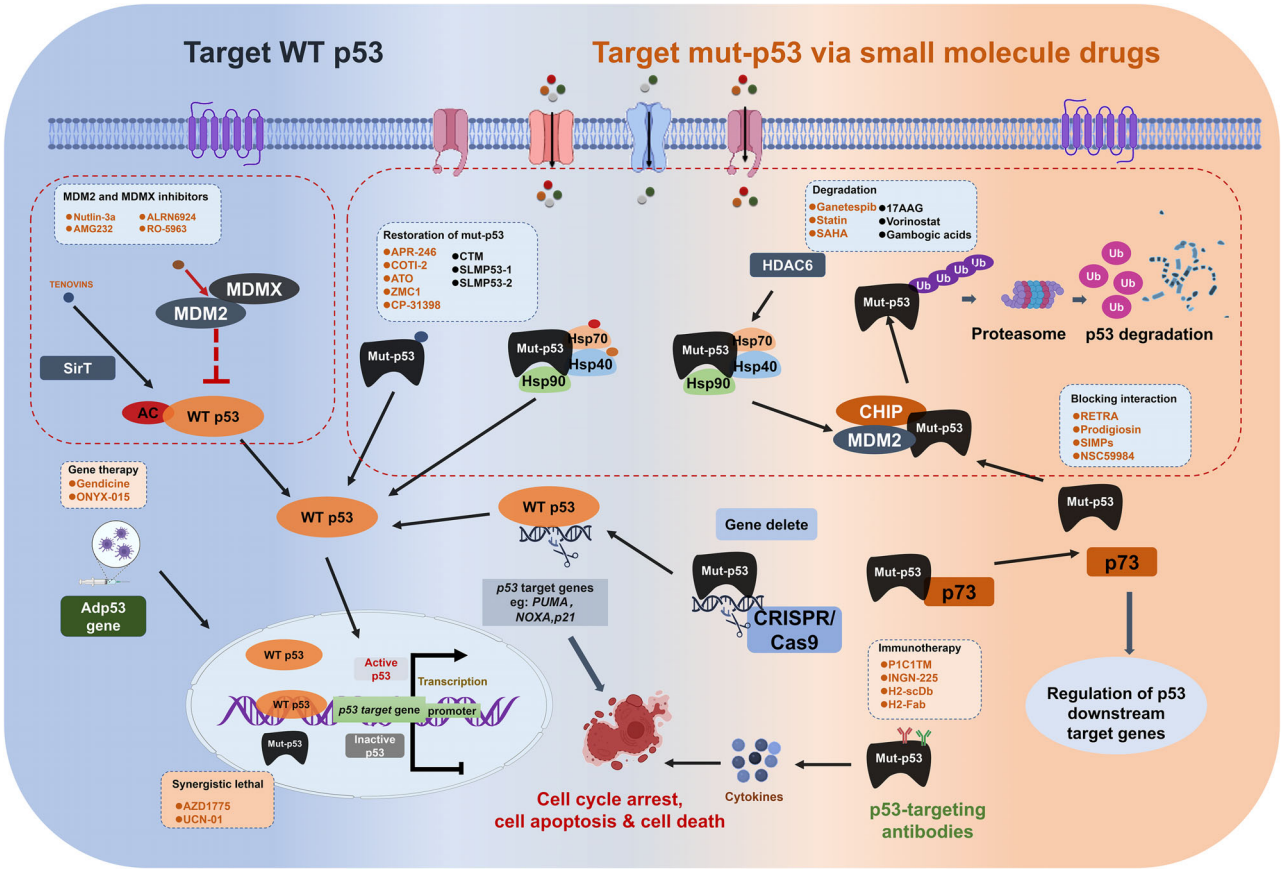

FIGURE 12 Strategies for targeting mut-p53 and WT p53 in cancer cells. Pharmacological approaches for targeting WT and mut-p53 in cancer cells are focused on small molecules (upper panel). Small molecules targeting WT p53 activation by binding to p53 (such as RITA), inhibition of MDM2/MDMX (such as the MDM2 inhibitor nutlin-3 and the dual inhibitor ALRN6924), and posttranslational modifications (such as TENOVIN) have been developed. Small molecules targeting mut-p53 via restoration of p53 function (such as PRIMA-1), degradation of mut-p53 via activation of MDM2 (such as 17AAG and NSC59984) or disruption of the mut-p53-p73 interaction (such as RETRA) have been developed. Activation of p73 upregulates p53 target gene expression and induces cell death. Biotherapeutic approaches are based on gene transfection and genomic modifications (bottom panel). p53 is transduced into cancer cells via an adenovirus (such as rADp53) to replace mut-p53 and thus upregulates p53 signaling. Genomic editing approaches (such as CRISPR) are used to restore WT p53 or delete mut-p53 in cancer cells. A bispecific antibody with a mut-p53-specific peptide and ALH ligands promotes the recognition and killing of p53-mutant tumor cells by T cells as an anticancer immunotherapeutic strategy. Data were retrieved from and based on reference [11, 14, 18, 79]. MDM2, Mouse double minute 2; MDMX, Mouse double-minute 4; Hsp40/70/90, heat shock protein 40/70/90; Ub, ubiquitin. RITA, reactivating p53 and Inducing Tumor Apoptosis; RETRA, Reactivation of Transcriptional Reporter Activity; 17AAG, 17-(allylamino)-17-demethoxygeldanamycin; WT, wild-type; PRIMA-1, p53 reactivation and induction of massive apoptosis-1; ALH, N-acyl homoserine lactone; rADp53, recombinant human p53 adenovirus; CHIP, hsp70-interacting protein; PUMA, P53 up-regulated modulator of apoptosis; NOXA, phorbol-12-myristate-13-acetate-induced protein 1

TABLE 1 Clinical trials targeting p53 in cancer therapy, sourced from the ClinicalTrials.gov database (https://clinicaltrials.gov/ct2/home)

Compound	Indication	Phase	Current status	NCT number	Trial title	Mechanism of actin	Brief Summary/Reference
RG7112 (RO5045337)	Advanced solid tumors, hematologic neoplasms and liposarcomas	I	Completed	NCT00559533 NCT01164033 NCT00623870 NCT01143740	A study of RO5045337 (RG7112) in patients with advanced solid tumors	Small-molecular MDM2 antagonist	NR, NA
RG7112 (RO5045337) with cytarabine	AML	I	Completed	NCT01635296	A study of RO5045337 in combination with cytarabine in patients with acute myelogenous leukemia	Small-molecular MDM2 antagonist	NR, NA
Idasanutlin (RG7388, RO5503781)	Multiple myeloma	I/II	Active, not recruiting	NCT02633059	Idasanutlin, ixazomib citrate, and dexamethasone in treating patients with relapsed multiple myeloma	Small-molecular MDM2 antagonist	NR, NA
MI-773 (SAR405838)	Neoplasm malignant	I	Completed	NCT01636479	Phase I safety testing of SAR405838	Small-molecular MDM2 antagonist	Safety profile with limited activity [564]
DS-3032b	Advanced solid tumor, lymphoma	I	Completed	NCT01877382	A Phase I multiple ascending dose study of milademetan in subjects with advanced solid tumors or lymphomas	Small-molecular MDM2 antagonist	NR, NA
AMG 232 (Navtemadlin)	Soft-tissue sarcomas	Ib	Active, not recruiting	NCT03217266	Navtemadlin and radiation therapy in treating patients with soft tissue sarcoma	Piperidinone inhibitor of MDM2-p53 interaction	NR, NA
AMG 232 (Navtemadlin)	Merkel cell carcinoma	Ib/II	Recruiting	NCT03787602	Navtemadlin (KRT-232) with or without anti-PD-1/anti-PD-L1 for the treatment of patients with merkel cell carcinoma	Piperidinone inhibitor of MDM2-p53 interaction	NR, NA
APG-115 (Alrizomadlin)	Melanoma and advanced solid tumors	Ib/II	Recruiting	NCT03611868	A Study of APG-115 in combination with pembrolizumab in patients with metastatic melanomas or advanced solid tumors	MDM2 inhibitor	NR, NA
APG-115 (Alrizomadlin)	Salivary gland cancer	I/II	Recruiting	NCT03781986	APG-115 in salivary gland cancer trial	MDM2 inhibitor	NR, NA
Siremadlin	AML	Ib/II	Recruiting	NCT05155709	A Study of siremadlin in combination with venetoclax plus azacitidine in adult participants with AML who are ineligible for chemotherapy.	Imidazopyrro-lidinone scaffold-based inhibitor of MDM2-p53 interaction	NR, NA
ASTX295	Advanced solid tumors with WT p53	I/II	Recruiting	NCT03975387	Study of ASTX295 in patients with solid tumors with WT p53	MDM2 inhibitor	NR, NA
ALRN-6924	Advanced solid tumors	Ib	Recruiting	NCT03725436	ALRN-6924 and paclitaxel in treating patients with advanced, metastatic, or unresectable solid tumors	MDM2/MDMX inhibitor	NR, NA
ALRN-6924	Pancreatic cancer	I	Recruiting	NCT03654716	Phase I study of the dual MDM2/MDMX Inhibitor ALRN-6924 in pediatric cancer	MDM2/MDMX inhibitor	NR, NA

(Continues)

TABLE 1 (Continued)

Compound	Indication	Phase	Current status	NCT number	Trial title	Mechanism of actin	Brief Summary/Reference
BI 907828	Glioblastoma	0/Ia	Recruiting	NCT05376800	A study to determine how BI 907828 is taken up in the tumor and to determine the highest dose of BI 907828 that could be tolerated in combination with radiation therapy in people with a brain tumor called GB	MDM2 inhibitor	NR, NA
MK-8242	Solid tumors, AML	I	Terminated	NCT01451437	Study of MK-8242 alone and in combination with cytarabine in participants with acute myelogenous leukemia (P07649)	MDM2 inhibitors	NR, NA
CGM097	Solid tumor with p53 WT status	I	Completed	NCT01760525	A phase I dose escalation study of CGM097 in adult patients with selected advanced solid tumors	MDM2 inhibitors	Improved PFS [565]
HDM201	Advanced soft-tissue sarcoma, metastatic soft-tissue sarcoma	I/II	Recruiting	NCT05180695	HDM201 and pazopanib in patients with p53 WT advanced/metastatic soft tissue sarcomas	MDM2 inhibitors	NR, NA
SGT-53	Pancreatic cancer	II	Recruiting	NCT02340117	Study of combined SGT-53 plus gemcitabine/Nab-paclitaxel for metastatic pancreatic cancer	Liposome complex encapsulating normal human WT p53 DNA in a plasmid backbone	NR, NA
PC14586	Advanced solid tumors with a p53 Y220C mutation	I/II	Recruiting	NCT04585750 NCT04585750	The evaluation of PC14586 in patients with advanced solid tumors harboring a p53 Y220C mutation	Structural corrector of p53 Y220C mutant protein	NR, NA
Arsenic trioxide (ATO)	AML/MDS	I	Recruiting	NCT03855371 NCT04869475 NCT04489706 NCT04695223	Combination of decitabine and ATO to treat AML/MDS expressing a classified type of mut-p53	Structural corrector of conformational p53 mutants	NR, NA
SSG	AML/MDS	II	Recruiting	NCT04906031	SS in MDS/AML with one of the 65 defined p53 mutations that can be functionally rescued by SSG	Structural corrector of temperature-sensitive p53 mutants	NR, NA
PRIMA-1^{MET} (APR-246)	High-grade serous ovarian cancer	Ib/II	Completed	NCT02098343	p53 suppressor activation in recurrent high grade serous ovarian cancer, a phase Ib/II study of systemic carboplatin combination chemotherapy with or without APR-246	Restoration of mut-p53	NR, NA
PRIMA-1^{MET} (APR-246)	AML/MDS	II	Completed	NCT03931291	APR-246 in combination with Azacitidine for *TP53* mutated AML or MDS following allogeneic stem cell transplant	Restoration of mut-p53	NR, NA
PRIMA-1^{MET} (APR-246)	MDS	III	Completed	NCT03745716	APR-246 & Azacitidine for the treatment of *TP53* mutant MDS (MDS)	Restoration of mut-p53	NR, NA

(Continues)

TABLE 1 (Continued)

Compound	Indication	Phase	Current status	NCT number	Trial title	Mechanism of actin	Brief Summary/Reference
PRIMA-1^{MET} (APR-246)	MDS/oligoblastic AML	I/II	Completed	NCT03072043	Phase 1b/2 safety and efficacy of APR-246 w/Azacitidine for tx of *TP53* mutant myeloid neoplasms	Restoration of mut-p53	Favorable outcomes with response rates for MDS (73%) and oligoblastic AML (64%) [566]
PRIMA-1^{MET} (APR-246)	AML/MDS	I/II	Unknown	NCT03588078	Study of the safety and efficacy of APR-246 in combination with Azacitidine	Restoration of mut-p53	Favorable outcomes with response rates for MDS (62%) and AML (33%) [567]
PRIMA-1^{MET} (APR-246)	AML/MDS in post-HCT maintenance therapy	II	Completed	NCT03931291	APR-246 in combination With Azacitidine for *TP53* mutated AML or MDS following allogeneic stem cell transplant	Restoration of mut-p53	Improved RFS [568]
PRIMA-1^{MET} (APR-246)	Advanced solid tumor (bladder, gastric, NSCLC, and urothelial)	I/II	Completed	NCT04383938	Phase I/II study of APR-246 in combination with pembrolizumab in subjects with solid tumor malignancies	Restoration of mut-p53	Well tolerated for the combination with pembrolizumab [569]
PEITC (phenethyl isothiocyanate)	Oral cancer	I/II	Completed	NCT01790204	A study of the effects of PEITC on oral cells with mut-p53	Restoration of mut-p53	NR, NA
COTI-2	Advanced or recurrent malignancies	I	Unknown	NCT02433626	Study of COTI-2 as monotherapy or combination therapy for the treatment of malignancies	Reactivation of mut-p53	NR, NA
Ganetespib	Epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer	I/II	Terminated	NCT02012192	GANNET53: Ganetespib in metastatic, mut-p53, platinum-resistant ovarian cancer	Degradation of mut-p53	Confirm safe use of the combination [570]
Atorvastatin	Solid tumor and relapsed AML, colorectal carcinoma, ulcerative colitis	I/II	Recruiting	NCT03560882 NCT04767984	A pilot trial of atorvastatin in tumor protein 53 (p53) -mutant and p53 wild-type malignancies; testing atorvastatin to lower colon cancer risk in longstanding ulcerative colitis	Degradation of mut-p53	NR, NA
Vorinostat	Advanced cancers	I	Completed	NCT02042989	MLN9708 and vorinostat in patients with advanced p53 mutant malignancies	Degradation of mut-p53	Limited effects [571]
Vorinostat	Advanced malignancies	I	Completed	NCT01339871	Study of pazopanib and vorinostat in patients with advanced malignancies	Degradation of mut-p53	Extended PFS [572]
AZD1775	Advanced gastric adenocarcinoma,	II	Completed	NCT02448329	Study of AZD1775 in combination with paclitaxel, in advanced gastric adenocarcinoma patients harboring *TP53* mutation as a second-line chemotherapy	Synthetic lethality to p53	NR, NA

(Continues)

TABLE 1 (Continued)

Compound	Indication	Phase	Current status	NCT number	Trial title	Mechanism of actin	Brief Summary/Reference
AZD1775	Small cell lung cancer	II	Completed	NCT02688907	Phase II, single-arm study of AZD1775 monotherapy in relapsed small cell lung cancer patients with MYC family amplification or CDKN2A mutation combined with *TP53* mutation	Synthetic lethality to p53	NR, NA
MK1775	Solid tumors	I	Completed	NCT00648648	A dose escalation study of MK-1775 in combination with either gemcitabine, cisplatin, or carboplatin in adults with advanced solid tumors (MK-1775-001)	Synthetic lethality to p53	NR, NA
AZD1775	Recurrent uterine serous carcinoma	II	Recruiting	NCT03668340	AZD1775 in women with recurrent or persistent uterine serous carcinoma or uterine carcinosarcoma	Synthetic lethality to p53	Significant activity (but p53 deficiency alone is not sufficient) [559]
Adavosertib	Platinum-resistant ovarian cancer	II	Completed	NCT02272790	Adavosertib plus chemotherapy in platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer	Synthetic lethality to p53	Some promising outcomes with carboplatin [573]
MK-1775	Refractory and resistant ovarian cancer	II	Active, not recruiting	NCT01164995	Study with Wee-1 inhibitor MK-1775 and carboplatin to treat p53 mutated refractory and resistant ovarian cancer	Synthetic lethality to p53	Enhance carboplatin efficacy [557]
MK-1775	Platinum-sensitive ovarian tumors	II	Completed	NCT01357161	A study of MK-1775 in combination with paclitaxel and carboplatin versus paclitaxel and carboplatin alone for participants with platinum-sensitive ovarian tumors with the *P53* gene mutation (MK-1775-004)	Synthetic lethality to p53	Modest clinical benefit with improved PFS [574]
MK-8242	Solid tumors, AML	I	Terminated	NCT01451437	Study of MK-8242 alone and in combination with cytarabine in participants with acute myelogenous leukemia (P07649)	MDM2 inhibitors	NR, NA
Lamivudine	Metastatic colorectal cancer	II	Active, not recruiting	NCT03144804	A phase II study of lamivudine in patients with p53 mutant metastatic colorectal cancer	Inhibition of LINE-1 upregulated by p53 loss	SD in 8 out of 32 cases [575]
Gendicine™ (Ad-p53)	Solid tumor, lymphoma	II	Recruiting	NCT03544723	Safety and efficacy of p53 gene therapy combined with immune checkpoint inhibitors in solid tumors	Gene therapy-based on oncolytic viruses	NR, NA
ONYX-015	Lip and oral cavity cancer, head and neck cancer, oropharyngeal cancer	I	Withdrawn	NCT00006106	ONYX-015 with cisplatin and fluorouracil in treating patients with advanced head and neck cancer	Gene therapy-based on oncolytic viruses	NR, NA

Abbreviations: AML, acute myeloid leukemia; HCT, hematopoietic stem-cell transplant; HGSOC, high grade serous ovarian cancer; MDS, myelodysplastic syndromes; NA, not applicable; NR, not reported; NSCLC, non-small cell lung cancer; OS, overall survival.; PFS, progression-free survival; RFS, relapse-free survival; SCLC, small cell lung cancer; SD, stable disease.

lethality, which is completely rescued by p53 deletion, suggesting that the main functions of these two proteins are to inhibit p53 [458–460]. In cancer cells carrying WT p53, the MDM2 and MDMX genes are frequently overexpressed through either gene amplification or transcriptional upregulation [461, 462]. Therefore, MDM2 and MDMX are good drug targets for cancer treatment, and small-molecule inhibitors of the MDM2-p53 PPI to reactivate the function of p53 have been developed as a novel approach for therapy in cancers with WT p53.

Nutlin-3a, developed by Roche, was the first identified MDM2 inhibitor. Nutlin-3a binds to MDM2 in the p53 interaction domain and blocks their interaction, resulting in p53 accumulation and increased transcriptional activity. Nutlin-3a has been shown to induce cell cycle arrest and apoptosis in cancer cells in vitro and xenograft tumors in vivo [463]. Studies by other groups have shown that Nutlin-3a has p53-independent effects on cells. For example, p73, retinoblastoma protein 1 (RB1), and E2F1 are degraded by MDM2 [464–466]. Nutlin-3a has demonstrated efficacy in killing cancer cells in vitro, but its poor pharmacological properties have hindered its further clinical development. RG7112 (RO5045337) is a second-generation Nutlin-3a compound developed by Roche and tested in clinical trials [467]. Compared with Nutlin-3a, RG7112 has a lower half maximal inhibitory concentration (IC50) in tumor cells and is more selective for MDM2 [468]. Two registered phase I therapeutic trials (NCT00623870 and NCT00559533) to determine the maximum tolerated dose of RG7112 in hematology and advanced solid tumors have been completed. However, RG7112 has not yet entered phase II or phase III clinical trials.

Currently, RG7388 (RO5503781, NCT03158389) is probably the most potent and selective Nutlin-3a derivative [469]. It was found to inhibit the growth of SJSA1 human osteosarcoma xenograft tumors (with WT p53) at a dose approximately 4 times lower than that of RG711242 [469]. Currently, there are 15 registered clinical trials of RG7112 either as monotherapy or in combination with other anticancer agents. The most advanced clinical trial of RG7112 is a phase III trial (NCT02545283) in patients with relapsed or refractory AML, in which patient recruitment is complete. The results of this trial are expected in the near future [470]. The primary aim of this trial is to evaluate the effect of RG7112 in combination with the chemotherapeutic drug cytarabine compared with cytarabine alone on the overall survival of patients with WT p53. Other companies or institutes have also developed MDM2 inhibitors, such as AMG232 (Kartos Therapeutics), SAR405838 (MI-77301, Sanofi), and MK-8242 (SCH-900242, Merck) [471]. These MDM2 inhibitors are also being evaluated in clinical trials for various types of cancers either alone or in combination with other agents.

Similar to MDM2, MDMX has also attracted considerable attention for inhibitor development, although fewer MDMX inhibitors have been identified to date. Most earlier efforts were devoted to designing stapled peptides to inhibit MDMX activity. Stapled peptides generally have an α-helical structure and a hydrocarbon bond (staple) between two nonadjacent amino acid residues. These hydrocarbon-stapled peptides have shown biological activity toward inhibiting PPIs [472]. Stapled peptides can target PPIs with greater specificity than small-molecule compounds because of their ability to bind to large PPI surfaces. In addition, stapled peptides do not generate toxic metabolic intermediates during their degradation, as most small-molecule compounds do. Therefore, stapled peptides offer a new therapeutic intervention. A highly specific stapled peptide (stabilized alpha helix of p53, SAH-p53-8) to inhibit the MDMX-p53 interaction has been designed [473]. SAH-p53-8 was found to activate p53 in MDMX-dependent cancer cells and induce apoptosis in vivo. It also inhibited tumor growth in a xenograft model established with JEG-3 cells. However, later studies showed that SAH-p53-8 binds with high avidity to serum, a property limiting its entry into tumor cells and thus its further clinical development [474, 475]. Based on a different peptide sequence, a dual-stapled peptide inhibitor of MDM2 and MDMX named ALRN-6924 was invented. ALRN-6924 simultaneously inhibits MDM2 and MDMX and has shown a promising antitumor effect in several xenograft models with overexpression of MDM2 or MDMX [476]. This dual inhibitor is being evaluated in 5 phase I and phase II clinical trials for AML and several solid tumors [14]. Additionally, recent work has found that combined use of inhibitors of MDM2 and phosphatase protein phosphatase magnesium-dependent 1 (PPMID) further enhances p53-dependent transcriptional activation, which in turn induces cell death and halts tumor growth in mice [477].

7.1.2 | Side effects of MDM2 and MDMX inhibitors

One interesting observation about MDM2 and MDMX inhibitors is that reactivation of p53 by these inhibitors is generally well tolerated by most normal tissues, although these tissues also express WT p53 [478]. In both xenograft mouse models and clinical trials, most normal tissues have seemed to have a higher threshold for p53-induced killing than tumor tissues [479]. This observation is supported by studies using genetically engineered murine models (GEMMs) in which WT p53 expression is restored in p53-defective tumor cells by genetic approaches [479–481]. In these whole-animal studies, restoration of WT p53 was

found to be well tolerated in normal tissues. The reason that WT p53 tumors are more sensitive to p53 reactivation than most normal tissues is incompletely understood. One possible explanation is that although the *TP53* gene is intact in WT p53 tumors, the activity of the p53 pathway is dysregulated. The survival signaling pathways in these tumor cells are thus significantly reprogrammed in such a way that confers addiction to downregulation of p53 activity. Therefore, p53 reactivation disrupts the reprogrammed survival pathways and causes cell death. The other possible explanation is that p53 has non-cell autonomous functions. In tumor settings, p53 activation affects the functions of tumor-infiltrating immune cells and/or stromal cells, which affect tumor growth. A third possible explanation is that p53 reactivation preferentially kills rapidly proliferating cells, such as cancer cells and certain blood cells. Indeed, the most common side effect of the MDM2 inhibitor RG7112 observed in clinical trials is hematological toxicity [482, 483]. Understanding the mechanism(s) underlying the preferential p53 activation in cancer cells may facilitate the development of better inhibitors with increased specificity and decreased side effects.

7.2 | Approaches to reactive mut-p53

As a result of its overexpression, mut-p53 also possesses toxic GOF properties that can propagate and cause malfunctions in other important proteins and pathways that regulate the cell cycle [484]. Considering the above factors, mut-p53 is an important pharmacological target, and the past two decades have seen considerable dedication to the development of small molecules aiming to restore WT function in mut-p53 [217, 485–489]. In particular, targeting mut-p53 specifically allows for a more selective approach in treating cancer cells, which in turn reduces the potential risk of side effects and toxicity in healthy tissues. The development of small molecules has utilized various mechanistic strategies, such as protein refolding through cysteine modification, protein stabilization, modulation of protein aggregation, and zinc chelation. These strategies will be discussed in detail below. [11, 14, 397].

7.2.1 | Protein refolding via cysteine modification

Cysteine reactivity plays an important role in many biological functions, including oxidatively controlled protein folding, and thus, thiol modification is a frequent target for medicinal chemists [490, 491]. CP-31398 is the first small molecule proven to reactivate mutant p53 (Figure 12). An earlier study reported that CP-31398 restores the native p53 conformation in cells with mut-p53, allowing transcriptional activation and slowing tumor progression in xenograft models [64]. Subsequent mechanistic studies revealed that the reactive double bond could function as a Michael acceptor. That is, it can participate in the Michael reaction, the conjugate addition of carbanions to α- and β-unsaturated aldehydes, ketones, carboxylic acids, esters, nitro compounds, and the like. At least part of its mechanism involves modification of p53 cysteine residues to promote refolding [492, 493]. CP-31398 is still being investigated in preclinical studies, but it has not advanced to clinical trials partially due to notable reports of p53-independent activities and multiple off-target effects [217]. A structurally related compound, STIMA-1, was later identified in a cell-based screen and is reported to act like a Michael acceptor to modify cysteines in an open pocket located in the DBD of p53 [492, 494]. Biological studies revealed that STIMA-1 has more potent activity toward mut-p53 in cancer cell lines than does CP-31398 in terms of activating apoptosis [217, 486]. PRIMA-1 and its more potent methylated analog PRIMA-1^{Met} (commonly referred to as APR-246; Figure 12) were discovered using a screen; these compounds restored WT function in the p53 mutants R175H and R273H and inhibited tumor growth in xenograft mice [495]. According to reports on APR-246′s mechanism of action, when hydrolyzed, it is converted to the active Michael acceptor methylene quinuclidinone (MQ), which covalently binds cysteine residues in p53, specifically Cys124 and Cys277, and facilitates its refolding into the active conformation [67]. APR-246 was the first p53-reactivating small molecule to enter clinical development and is currently in phase II clinical studies [485]. Bykov *et al.* [496] a demonstrated that the maleimide-derived molecule MIRA-1 also can reactivate DNA binding and preserve the active conformation of mutant p53 protein in vitro and restore transcriptional transactivation to mutant p53 in living cells. This compound was chosen for further derivatization due to its selective activity toward cancer cells with mut-p53 (R273H) over those with WT p53 and its ability to upregulate p53 target genes and restore apoptotic activity. Similar to APR-246, MIRA-1 functions via Michael addition to covalently bind cysteines and promote protein refolding. Computational studies have shown that this compound primarily targets an open pocket in p53 between loops L1 and L3, which contain Cys124, Cys135, and Cys141 as potential targets [494]. Interestingly, the 3,4 double bond is imperative for its activity, as the analog MIRA-2 also displays mut-p53-dependent activity, whereas the saturated analogs (such as MIRA-A) are inactive [496]. Despite its initial promise, however, MIRA-1 exhibited high cytotoxicity in normal cell lines, demonstrating a mut-p53-independent mechanism [497].

7.2.2 | Restoring the zinc-binding ability of mut-p53

Zinc is crucial to the structural stability of p53 and plays a major role in preserving its folded structure and facilitating its DNA binding [498]. At physiological temperatures, mutants that perturb the zinc-binding site and result in apo (zinc-free) p53 are primarily unfolded, are prone to aggregation, and result in loss of sequence-specific DNA binding [499]. Interesting reports have demonstrated that manipulation of intracellular zinc concentrations can change the structure and function of p53, alluding to the reversible nature of the protein's folding [500]. Specifically, Hainaut *et al.* [501] demonstrated that the addition of zinc chelators to cells and cell lysates to deplete p53 of zinc reduces its ability to be recognized by WT-specific antibodies and increases its recognition by a mutant-specific antibody. This process can be reversed by supplementing the cell culture medium with $ZnCl_2$. In fact, Puca *et al.* [502] showed that treatment with $ZnCl_2$ restores native p53 folding and WT transcriptional activity in zinc binding-defective mutants. While high concentrations of $ZnCl_2$ can be harmful to the cell [503], this finding highlights the potential clinical applications of restoring zinc-binding ability in mut-p53. This group has since designed a series of fluorescent zinc-curcumin complexes that restore the native folding conformation and induce functional activation in zinc binding-deficient p53 mutants (such as R175H and R273H) [504, 505]. Substantial research attention has been devoted to the design of small molecules that act as metallochaperones to restore native zinc binding in mut-p53 [500].

In addition, given that insufficient levels of zinc result in protein misfolding and impaired DNA binding, the first criterion is that a metallochaperone must increase the intracellular level of Zn^{2+} to repopulate the metal-depleted mut-p53 site [506]. Blanden *et al.* [500] revealed features that are critical when designing zinc metallochaperones for mut-p53. While the majority of intracellular zinc is bound to cytosolic Zn-binding proteins, the concentration of the pool of "free Zn^{2+}" is estimated to be in the nanomolar to picomolar range [507]. However, reports have also demonstrated that excess zinc induces p53 misfolding via the binding of zinc to non-native amino acids located near the zinc-binding site [508]. In addition, in 2018, the US FDA approved arsenic trioxide (As_2O_3) to treat APL. Similar to Zn^{2+}, the arsenic ion coordinates to thiolate groups of cysteines, and As_2O_3 exerts its anti-APL effects by replacing Zn^{2+} with As^{3+} in the RING domain of PML-RARα, a protein chimera with oncogenic function [509]. In 2021, Chen *et al.* [70] reported that As_2O_3 rescued multiple p53 hotspot mutants, including R175H, R248Q, R175L, G245S, and R249S. ATO was identified in a multitier screen for compounds that were likely to bind to multiple cysteine residues, such as PML-RARα. It was hoped that the arsenic ion would bind to the same residues as Zn^{2+} but with higher affinity, and in the case of p53, increase its thermodynamic stability while allowing it to remain functional. Surprisingly, arsenic did not displace zinc but was instead found to bind in a second, buried pocket in the DBD composed of 3 non-zinc-coordinating cysteine residues (C124, C135, and C141) and M133. These findings suggest a mode of action similar to that of PC14586 but applicable to a variety of mutants and not just Y220C. ATO has been shown to be synergistic with decitabine in vitro [510], and a phase I clinical trial is currently underway in which the 2 agents are being tested in high-risk MDS patients with mut-p53 (NCT03855371).

7.2.3 | Multifunctional ligand design

Structural mutations in the DBD of p53 destabilize the local environment, causing protein unfolding and aggregation. An estimated 30% of p53 mutants are temperature sensitive, with the protein unfolded and inactive at physiological temperatures yet exhibiting the native conformation to induce functional DNA binding and transcriptional activity upon a decrease to subphysiological temperatures [511, 512]. Thus, researchers have proposed that small molecules that selectively bind to the folded conformation with respect to unfolded conformations should shift the equilibrium toward a folded and active WT protein conformation [511]. In one of the most common thermally unstable mutants, p53-Y220C, the substitution of a large tyrosine to a smaller cysteine creates an open cavity at the surface of the protein, lowering its stability and causing unfolding of 80% of the DBD [513, 514]. Baud *et al.* [515] generated a library of small molecules that target the mutation-induced cavity of p53-Y220C to increase its stability and restore WT function. By in silico methods and fragment-based screening, the first such compound discovered was PhiKan083. This compound, featuring a carbazole core, exhibited moderate binding affinity (150 mmol/L) to the p53-Y220C mutant and thermally stabilized the protein by increasing its melting temperature [516]. PhiKan7088 also exhibited modest binding affinity within the p53-Y220C mutant activity (140 mmol/L) and was shown to refold mut-p53 in experiments with conformation-specific antibodies, as well as activate p53-dependent apoptosis and cell cycle arrest [517].

7.2.4 | Modulating mut-p53 aggregation

Amyloidogenic proteins are prone to endogenous misfolding and prion-like conversion from a soluble, folded protein into alternative oligomeric and fibrillar structures

[518–520]. Proteins characterized by this feature include amyloid-β, tau, transactive response DNA binding protein of 43 kDa (TDP-43), and superoxide dismutase 1 (SOD1), and these proteins contribute to a wide range of diseases, including Alzheimer's disease [521, 522] and amyotrophic lateral sclerosis (ALS) [523].

Mut-p53 aggregates are not only characterized by LOF but also have been extensively characterized to possess toxic GOF properties by self-propagating and cross-reacting with other proteins to further enhance aggregation [216, 524]. Most notably, mut-p53 aggregates can coaggregate with homologous proteins such as p63 and p73 to form amyloid oligomers and fibrils and thereby inhibit the function of the p53 proteins, which has led to the classification of p53 mutant-based cancers as an amyloid disease [525, 526]. This classification of p53 as an amyloidogenic protein, however, is relatively recent, and important information elucidating the detailed mechanisms of p53 aggregation and GOF effects remains to be discovered [527]. Thus, this classification is often overlooked by cancer and amyloid researchers alike, and the field thus remains in relative infancy [527]. However, the involvement of p53 aggregates in cancer development has been well documented, and amyloid aggregates have been identified in patient biopsies of various cancers and are associated with more aggressive and invasive tumors [214, 528, 529]. This highlights the importance and need for small molecules aimed at disrupting p53 aggregation and preventing its GOF effects. A recent seminal study involving not a small molecule but a small cell-penetrating peptide sequence, ReACp53, pioneered the concept that modulating p53 aggregation is a viable option for restoring p53 function. The peptide sequence of ReACp53 closely mimics that of the aggregation-prone region encompassing amino acids 252-258 with the LTIITLE sequence in p53 and reduces the aggregation of p53 in cells, thereby alleviating its toxic GOF effects. This effect was found to result in upregulation of p63 expression, lead to functional rescue of the p53 mutants R175H and R248Q via induction of apoptosis, and decrease tumor proliferation in xenograft models [214].

7.3 | Approaches to eradicate cells with mut-p53

Numerous studies have elucidated the roles of p53 in tumor progression since its discovery 40 years ago. However, mutant forms of the tumor suppressor p53 not only lose their tumor-suppressive properties but also frequently acquire tumor-promoting properties [25]. The development of p53-targeted drugs is particularly difficult because the agent must specifically target mut-p53 in cancer cells while having no effect on normal cells harboring WT p53 [530]. Additionally, multiple p53 mutations result in various mut-p53 protein structures that are difficult to target [63]. The major therapeutic strategies targeting p53 can be classified into multiple categories based on the p53 status that they target: strategies that restore WT p53 functions and those that eradicate mut-p53 [531–534] (Figure 12 and Table 2).

7.3.1 | Mut-p53 degradation agents

One important strategy for targeting p53 mutants is to reduce their stability. This strategy is based on the concept of oncogene addiction. Oncogene addiction is the phenomenon in which some cancer cells, despite their complex genetic and epigenetic alterations, rely on a single oncogene or small set of oncogenes for survival or growth [535]. As described above, certain p53 mutants are pro-oncogenic [531, 536, 537]. In cancer cells addicted to mut-p53, a reduction in mut-p53 levels causes the death of these cells. The stability of mut-p53 is enhanced by heat shock proteins (HSPs), such as HSP90 and HSP70, and their cofactor histone deacetylase 6 (HDAC6) [538, 539]. Binding of the HSP complex prevents the degradation of mut-p53 mediated by the ubiquitin E3 ligases MDM2 and CHIP [540, 541]. HSP inhibitors such as geldanamycin have been shown to destabilize mut-p53 [542]. Treating xenograft mice carrying germline p53 R172H or R248Q mutations with the HSP90 inhibitor ganetespib or alvespimycin (17DMAG) plus SAHA (a histone deacetylase inhibitor) significantly extended the life span of these mice, suggesting that HSP inhibition is a feasible strategy to target mut-p53 [543, 544]. HSP inhibition has been investigated in clinical trials, although to date, none of the tested HSP inhibitors have received US FDA approval [543, 544]. Notably, HSPs have many clients in addition to mut-p53. Indeed, the stability of WT p53 is also regulated by HSPs. Therefore, HSP inhibition has pleiotropic effects on cancer cells [545], and the p53 mutation status alone may not be a good predictor of the clinical benefits of HSP inhibitors. As described above, MDM2 inhibitors are being evaluated in clinical trials to inhibit WT p53 tumors. However, the role of MDM2 in the degradation of mut-p53 creates a challenge for the use of these inhibitors, because they may promote tumorigenesis and/or metastasis in tumors carrying mut-p53. This idea was supported by the findings of a study by Terzian *et al.* [546]. Using a GEMM of the p53 R172H mutant (in humans), they found that MDM2 deletion in the context of R172H mutant expression promoted tumorigenesis and metastasis. It would be intriguing to investigate in future clinical trials whether prolonged treatment with MDM2 inhibitors leads to the selection

TABLE 2 Small-molecule drugs targeting mut-p53 or WT p53 in preclinical studies

Role	Compound	Mechanism of actin	Clinical development status	References
p53 activator	RITA	Binds to p53 and prevents WT p53 degradation by blocking its interaction with MDM2	Experimental and/or preclinical	[576]
MDM2 inhibitor	Nutlin-3a	Blocks the interactive binding sites of p53 and MDM2, dramatically increasing the half-life of p53 and activating p53-mediated transcription	Experimental and/or preclinical	[18, 463, 577]
MDM2/MDMX (MDM4) dual inhibitor	RO-5963 RO-2443	Blocks the interactive binding sites of p53 and MDM2/MDMX (MDM4), dramatically increasing the half-life of p53	NA	[578]
MDM2 degrader	PROTAC 8	Targeted degradation of MDM2 using PROTACs	Experimental and/or preclinical	[579]
	A1874			
Mut-p53 restoration agent	CP-31198	Cysteine-binding compounds; Michael acceptor binding to mut-p53	Experimental and/or preclinical	[64]
	PRIMA-1	Cysteine-binding compound converted to MQ, which binds mut-p53 by Michael addition	Experimental and/or preclinical	[495]
	MIRA-1	Michael acceptor binding to mut-p53	Experimental and/or preclinical	[496]
	STIMA-1	Michael acceptor binding to mut-p53	Experimental and/or preclinical	[492, 580, 581]
	3-benzoylacrylate acid	Binds to mut-p53 by Michael addition	Experimental and/or preclinical	[580, 582]
	KSS-9	Microtubule poison; redox; Michael acceptor binding to mut-p53	Experimental and/or preclinical	[583]
	PK1107	Binds to mut-p53 by nucleophilic aromatic substitution	Experimental and/or preclinical	[581]
	ZMC1, ZMC2, ZMC3, ZN-1	Zn^{2+} chelators	Experimental and/or preclinical	[44]
	Chetomin	Promotes Hsp40 expression and p53-Hsp40 binding to restore WT p53 conformation	Experimental and/or preclinical	[584]
	SLM P53-1	Restores wild-type-like DNA binding ability to mut-p53 R280K Bridges extra interaction between p53 and DNA that rescues DNA binding and transcriptional activity	Experimental and/or preclinical	[585, 586]
	SLM P53-2	Restores the WT-like conformation and DNA-binding ability, possibly by enhancing the interaction with Hsp70.	Experimental and/or preclinical	[587]
	SCH529074	Enables mut-p53 to bind to a consensus p53 DNA-binding site	Experimental and/or preclinical	[588]
	WR1065	Restores temperature-sensitive mut-p53 native conformation	Experimental and/or preclinical	[589]
	Adamantyl isothiocyanates	Rescues mut-p53 R206K and R273H and results in upregulation of canonical WT p53 targets and ATM phosphorylation	Experimental and/or preclinical	[590]
	Stictic acid	Blocks the pocket between loop L1 and sheet S3 of the p53 core domain and re activates mut-p53	Experimental and/or preclinical	[494]
	MB725	Binds to Y220C in the p53 DBD and stabilizes mut-p53	NA	[72, 511, 515]
	MB710			
	PK083			
	PK9318			
	PCAPs	Binds to mut-p53 and promotes refolding	Experimental and/or preclinical	[591]

(Continues)

TABLE 2 (Continued)

Role	Compound	Mechanism of actin	Clinical development status	References
	Butein	Restores the ability of mut-p53 to bind DNA by reversing its transition to the L3 state	Experimental and/or preclinical	[592]
Mut-p53 degradation agent	Gambogic acid	Increases WT p53 proteins levels, inhibits mut-p53-Hsp90 complexes and induces CHIP-mediated degradation	Experimental and/or preclinical	[593]
	Onalespib	HSP90 inhibitors or statins depleting mut-p53	Experimental and/or preclinical	[594, 595]
	Luminespib			
	TAS-116			
	Torvastat	HDAC inhibitor, destabilizes mut-p53 through inhibition of the HDAC6-HSP90 chaperone axis, and, simultaneously inhibit the transcription of mut-p53 through HDAC8	Experimental and/or preclinical	[596, 597]
	Lovastatin	Statin drugs: inhibits the mevalonate pathway	Experimental and/or preclinical	[598]
	Disulfiram (DSF)	Catalyzes the degradation of both WT p53 and mut-p53 through the 26S proteasome pathway	Experimental and/or preclinical	[599]
	Buxus alkaloid	Destabilizes mut-p53 through inhibition of the HSF1 chaperone axis	Experimental and/or preclinical	[600]
	NSC59984	Promotes MDM-mediated mut-p53 protein degradation and stimulates p73	Experimental and/or preclinical	[601]
	Spaurtin-1	Target the CMA pathway	Experimental and/or preclinical	[602]
	Reacp53	Disrupts mut-p53 aggregates	Experimental and/or preclinical	[214]
Disruption of mut-p53's GOF	RETRA	Binds to mut-p53 and disrupts mut-p53-p73 complexes	Experimental and/or preclinical	[603]
	Prodigiosin	Disrupts mut-p53-p73 complexes	Experimental and/or preclinical	[604]
Immunotherapy	H2-scDb H2-Fab	Bispecific antibody linking T cells to cancer cells with one arm binding to the T cell receptor and the other to the HLA-mut-p53 R175H peptide on the cancer cell surface.	Experimental and/or preclinical	[439]

Abbreviations:WT, ATM, ataxia-telangiectasia mutated; CMA, chaperone-mediated autophagy; DBD, DNA-binding domain; HDAC, histone deacetylase; HSF1, heat shock factor 1; L3, Loop3; MDM2, murine double minute 2; MQ, methylene quinuclidinone; NA, not applicable; PROTAC, proteolysis targeting chimera.;wide type.

of p53 mutant clones that exhibit greater aggressiveness compared to WT p53 clones.

7.3.2 | Gene therapy

Since most cancer cells have a defective p53 signaling pathway, a straight forward concept is the transduction of WT p53 back into cancer cells. The reconstituted WT p53 will then lead to tumor regression. This concept led to the development of a recombinant adenovirus expressing WT p53 (rAd5-p53; Gendicine™), which received approval by the Chinese Food and Drug Administration in 2003 for treating head and neck carcinoma [378]. Reports also showed clinical benefits of Gendicine™ in other types of cancers [530]. Gendicine™ is often cited as the first gene therapy. A similar virus (Advexin) developed by Introgen Therapeutic, Inc, however, failed to receive approval from the US FDA in 2008. Recently, another similar adenovirus expressing p53 (Ad-p53), developed by MultiVir, is in a clinical trial in combination with immune checkpoint inhibitors for recurrent or metastatic head and neck cancer (NCT03544723).

Another type of viral gene therapy related to p53 is oncolytic adenoviruses. Several DNA viruses encode oncoproteins that inactivate p53, such as polyomavirus SV40 large T-antigen, adenovirus E1B, and HPV. A mutant adenovirus called ONYX-015, in which the E1B gene is deleted, was developed in an attempt to specifically kill tumor cells carrying defective p53 (mutated or deleted) [63]. The rationale behind ONYX-015′s putative specificity for p53-defective cancer cells is that it will rapidly amplify in these cells and eventually lyse the cells due to the cell cycle arrest and apoptosis defects caused by p53 functional deficiency [547]. On the other hand, in cancer cells or normal cells carrying WT p53, the virus cannot efficiently replicate because WT p53 elicits stress responses and limits the spread of the virus. Notably, the specificity of ONYX-015 for killing cancer cells with defective p53 remains controversial. Some reports have supported the concept of selectivity, while others have shown that ONYX-015 kills cancer cells regardless of the p53 status [63, 532–534, 548]. Some reports have even shown the opposing finding that p53 is required for the cytotoxic effects of ONYX-015 [548, 549]. The clinical development of ONYX-015 was suspended due to financial reasons. However, a similar oncolytic adenovirus called H101 was approved by the Chinese FDA in 2005 to treat head and neck cancer [550], but like rAd5-p53, H1010 has not received clinical approval for cancer treatment outside of China.

In theory, reintroduction of WT p53 may also inhibit certain tumors carrying the WT p53 gene. As described above, although these tumors have intact p53, the activity of the p53 pathway may be dysregulated, for example, through overexpression of its negative inhibitors MDM2 and MDMX. A common issue for virus-based gene therapies targeting p53 is delivery efficiency. Since not every cell in a tumor is virally transduced, tumor relapse is very common after treatment [550].

Although intact p53 is present in some cancers, this tumor suppressor is still inhibited via various mechanisms. MDM2 is the major negative regulator of p53, preventing p53 from entering the nucleus, reducing its DNA-binding ability, and promoting its proteasomal degradation [29, 30]. Genetic amplification is the most frequent genomic alteration of MDM2 and was first found in soft tissue sarcoma [31]. Amplification and overexpression of MDM2 were mutually exclusive with p53 mutation [32]. el-Deiry *et al.* [33] discovered that MDM2 overexpression involved intact p53 across numerous cancer types in a study using The Cancer Genome Atlas (TCGA) database. Thus, inhibiting MDM2 expression in cancers with WT p53 is an intriguing therapeutic strategy that has been successfully applied in clinical settings (Table 1). Since the discovery of a class of cis-imidazoline analogs called nutlins (e.g., nutlin-3a) that inhibit p53-MDM2 binding, MDM2 inhibitors have been extensively studied as a targeted treatment for patients with WT p53 [12, 34]. Nutlin-3a, a preclinical drug, inhibits tumor growth by reactivating WT p53, either alone or in combination with other therapies [35–37]. Due to the promising results of in vitro studies, clinical trials were conducted to assess the efficacy and safety of RG7112 (RO5045337), a derivative of nutlin-3a [38].

7.3.3 | Synthetic lethality of p53 loss

As described above, targeting the GOF activities of p53 mutants is extremely challenging due to the diverse and context-dependent mechanisms of these GOF activities. Another strategy is to exploit synthetic lethality mechanisms in cancer cells carrying *TP53* mutations. The basis of synthetic lethality is that cancer cells develop 2 compensatory survival pathways. Removal of either pathway does not kill the cell while simultaneous deletion of the two pathways (synthetic) causes cell death (lethality) [551]. A clinically proven example of synthetic lethality in cancer treatment is the use of PARP inhibitors in BRCA1- or BRCA2-defective breast and ovarian cancers. PARP is involved in repairing single-strand breaks [552]. When PARP is inhibited, single-strand breaks progress to DSBs. In cells with BRCA1 and BRCA2 proficiency, these DSBs are repaired by BRCA1 and BRCA2, and the cells survival. However, in cells with defective BRCA1 and BRCA2, unrepaired DSBs result in cell death [553]. Therefore, synthetic lethality is extremely useful for exploiting the loss

of a tumor suppressor, and synthetic lethality screens have been performed in cancer cells with *TP53* mutations or deletions. In a study using a computational approach in the NCI-60, TCGA, and cancer cell line encyclopedia (CCLE) datasets, candidates showing synthetic lethality with p53 loss were identified, for example, polo-like kinase 1 (PLK1), polo-like kinase 4 (PLK4), CDK1, CDK16, mTOR, and aurora kinase A (AURKA) [554]. In an RNAi kinomics viability screen in head and neck squamous cell carcinoma cells, several kinases, such as Wee1-like protein kinase (WEE1), AURKA, and FYN, were found to be synthetically lethal with p53 [555]. The WEE1 inhibitor MK-1775 was selected for further preclinical studies and showed activity both as a single agent and in combination with cisplatin in p53-mutated head and neck tumors [556]. Phase I and II clinical trials using another WEE1 inhibitor, AZD1775, either as a monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, have shown clinical benefits in patients with advanced solid tumors [557]. Although these phase I and II trials were completed in 2015, no registered phase III clinical trial has been initiated.

As cancer genomes are extremely genetically and epigenetically heterogeneous, the genes synthetically lethal with p53 are likely cell type- and tissue type-dependent. Due to throughput limitations, most synthetic lethality screens have been performed in limited panels of cell lines. Therefore, whether the hits from these screens are cell type-specific remains unclear. Thus, future screens using more diverse cell lines are needed to identify genes with more general synthetic lethality with p53.

8 | CONCLUSIONS AND FURTHER PERSPECTIVES

Although constant progress is being made towards better p53-based cancer therapy, many challenges remain, and the search for efficient and selective drugs that will eventually be able to enter the clinic is still ongoing. One of the major challenges in targeting protein reactivation is the lack of a well-established mechanism. Additionally, the smooth surface structure of the protein makes it difficult to identify drug targeting pockets, with the exception of Y220C [558]. This lack of drug targeting capability is a significant obstacle. Furthermore, drug resistance is a common issue with p53-based therapies, as is the case with other antitumor therapies. Empirical-based knowledge on p53 mutations is limited, and its heterogeneity (WT, structural, DNA contacting, and others) contributes to tumorigenesis [12]. Current drugs targeting mutated p53 only address specific mutation types, leading to off-target effects. The accumulation of p53 in normal tissues can lead to toxic side effects, which is one of the main reasons why it is challenging to develop p53 as a drug [190].

For p53-targeted therapy, several other factors also need to be considered. First, *TP53* mutations are heterogeneous, and not all mutations are equal. Therefore, a one-drug-fits-all approach may not be feasible for targeting *TP53* mutations. Hence different *TP53* mutations may require different p53-targeting drugs [14]. Second, p53-based drugs are unlikely to enter the clinic as single therapies. Many studies have attempted to identify promising combinations of related drugs, such as simultaneous blockade of the MDM2-p53 pathway and the p53-Bcl-2 pathway, that may have synthetic lethal mechanisms [559]. In addition, as discussed earlier in the article, combining p53 activation with chemotherapy, RT, and immunotherapy is also appealing. Such combined treatments might reduce the required doses and may even overcome resistance in some instances.

Another concern arises from the fact that the in vivo testing of p53-based drugs is performed primarily in mouse models. Although mouse models remain a standard tool for drug discovery, many differences exist between mice and humans, including interspecies differences in the sequences of the p53, MDM2, and MDM4 proteins, as well as differences in the p53 signaling pathway. Advanced experimental methodologies, such as organoid cultures [560] and other *ex vivo* models (such as cell line derived xenograft [CDX] and patient derived xenograft [PDX]) [71, 560, 561], which are expected to become increasingly useful in bypassing these interspecies differences, provide a theoretical basis for accelerating the translation of p53-targeted drugs to the clinic. The complete structure of p53 in complex with various DNA targets and partner proteins is yet to be determined. However, certain p53 mutants cannot be expressed, and therefore their structures are not available, which limits the potential for structure-based drug design. Fortunately, advances in cryo-electron microscopy and AI offer promising avenues for further research and will likely provide a structural basis for future studies of p53 and the development of drugs that target it. Similarly, in recent years, gene editing technologies, such as mRNA vaccines, CRISPR-Cas9, and viral infections, have played a crucial role in disease treatment. For example, the development of mRNA vaccines in recent years has revolutionized cancer treatment. It is believed that in the future, vaccine strategies developed based on p53 mRNA may bring significant benefits in immunotherapy. However, further research is still required to uncover novel functions about p53 in the TIME. To sum up, these strategies can be used to correct mutations in the *TP53* gene, which may prove to be an effective option for future cancer treatment.

For decades, there has been a lack of effective progress in the development of drugs targeting p53, and p53 was

once considered to be an undruggable target. With several technological advances, many undruggable targets are becoming druggable. The high frequency of *TP53* mutations in human cancers suggests that drugs targeting p53 have the potential to revolutionize cancer treatment. However, due to our limited understanding of human biology and the intricate processes that occur within cancer cells after drug administration, there are still many unanswered questions that require further exploration. For example: (1) What are the biophysical, biochemical, and atomic details underlying the actions of p53 alone and in complex with MDM2/MDMX? (2) Is p53 clinically druggable? (3) Can p53 activity be analyzed by imaging in cells, tissues, and even animals? (4) Is p53 a metabolic regulator, a guardian of the genome, or both in all cells and tissues? (5) What levels of p53 expression are enough and too high? (6) Can AI be used to model the biological function of p53 in cells or in vivo? (7) Do p53 molecules in different cells or tissues physiologically communicate with one another in vivo, and if so, how? As the most frequently mutated protein in cancer therapy, p53 is often referred to as the "proverbial holy grail" for targeted drugs. However, recent developments in KRAS inhibition offer some hope. Like p53, KRAS has been deemed difficult to target due to repeated failures, but exciting progress has been made in this area. The recent US FDA approval of a specific KRAS(G12C) inhibitor has raised hopes that other challenging targets [562, 563], such as p53, may also achieve success in the future.

AUTHOR CONTRIBUTIONS

Bin Song and Ping Yang designed and prepared the manuscript. Bin Song and Shuyu Zhang drew and revised the figures. Bin Song and Shuyu Zhang revised the manuscript and supervised the manuscript preparation. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

1. Stratton MR, Campbell PJ, Futreal PA. The cancer genome. Nature. 2009;458(7239):719-724.
2. Stratton MR. Exploring the genomes of cancer cells: Progress and promise. Science. 2011;331(6024):1553-1558.
3. Martínez-Jiménez F, Muiños F, Sentís I, Deu-Pons J, Reyes-Salazar I, Arnedo-Pac C, et al. A compendium of mutational cancer driver genes. Nat Rev Cancer. 2020;20(10):555-572.
4. Sammons MA, Nguyen TAT, McDade SS, Fischer M. Tumor suppressor p53: From engaging DNA to target gene regulation. Nucleic acids research. 2020;48(16):8848-8869.
5. Sullivan KD, Galbraith MD, Andrysik Z, Espinosa JM. Mechanisms of transcriptional regulation by p53. Cell death and differentiation. 2018;25(1):133-143.
6. Levine AJ, Oren M. The first 30 years of p53: Growing ever more complex. Nature Reviews Cancer. 2009;9(10):749-758.
7. Levine AJ. p53: 800 million years of evolution and 40 years of discovery. Nat Rev Cancer. 2020;20(8):471-480.
8. Fuchs SY, Adler V, Buschmann T, Wu X, Ronai Z. Mdm2 association with p53 targets its ubiquitination. Oncogene. 1998;17(19):2543-2547.
9. Nag S, Zhang X, Srivenugopal KS, Wang MH, Wang W, Zhang R. Targeting MDM2-p53 interaction for cancer therapy: Are we there yet? Curr Med Chem. 2014;21(5):553-574.
10. Leng RP, Lin Y, Ma W, Wu H, Lemmers B, Chung S, et al. Pirh2, a p53-Induced Ubiquitin-Protein Ligase, Promotes p53 Degradation. Cell. 2003;112(6):779-791.
11. Wang Z, Strasser A, Kelly GL. Should mutant TP53 be targeted for cancer therapy? Cell Death Differ. 2022;29(5):911-920.
12. Kennedy MC, Lowe SW. Mutant p53: It's not all one and the same. Cell Death Differ. 2022;29(5):983-987.
13. Pavlakis E, Neumann M, Stiewe T. Extracellular Vesicles: Messengers of p53 in Tumor-Stroma Communication and Cancer Metastasis. Int J Mol Sci. 2020;21(24):9648.
14. Hassin O, Oren M. Drugging p53 in cancer: One protein, many targets. Nat Rev Drug Discov. 2023;22(2):127-144.
15. Kim MP, Lozano G. Mutant p53 partners in crime. Cell Death Differ. 2018;25(1):161-168.
16. Boutelle AM, Attardi LD. p53 and Tumor Suppression: It Takes a Network. Trends Cell Biol. 2021;31(4):298-310.
17. Kastenhuber ER, Lowe SW. Putting p53 in Context. Cell. 2017;170(6):1062-1078.
18. Duffy MJ, Synnott NC, O'Grady S, Crown J. Targeting p53 for the treatment of cancer. Semin Cancer Biol. 2022;79:58-67.

19. Sullivan KD, Galbraith MD, Andrysik Z, Espinosa JM. Mechanisms of transcriptional regulation by p53. Cell Death Differ. 2018;25(1):133-143.
20. Liu Y, Leslie PL, Zhang Y. Life and Death Decision-Making by p53 and Implications for Cancer Immunotherapy. Trends Cancer. 2021;7(3):226-239.
21. Hafner A, Bulyk ML, Jambhekar A, Lahav G. The multiple mechanisms that regulate p53 activity and cell fate. Nat Rev Mol Cell Biol. 2019;20(4):199-210.
22. Xiao J, Zhou J, Fu M, Liang L, Deng Q, Liu X, et al. Efficacy of recombinant human adenovirus-p53 combined with chemotherapy for locally advanced cervical cancer: A clinical trial. Oncol Lett. 2017;13(5):3676-3680.
23. Chen F, Wang W, El-Deiry WS. Current strategies to target p53 in cancer. Biochemical Pharmacology. 2010;80(5):724-730.
24. Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. Nature. 1979;278(5701):261-263.
25. Linzer DI, Levine AJ. Characterization of a 54K dalton cellular SV40 tumor antigen present in SV40-transformed cells and uninfected embryonal carcinoma cells. Cell. 1979;17(1):43-52.
26. Finlay CA, Hinds PW, Levine AJ. The p53 proto-oncogene can act as a suppressor of transformation. Cell. 1989;57(7):1083-1093.
27. Eliyahu D, Michalovitz D, Eliyahu S, Pinhasi-Kimhi O, Oren M. Wild-type p53 can inhibit oncogene-mediated focus formation. Proc Natl Acad Sci U S A. 1989;86(22):8763-8767.
28. Sabapathy K, Lane DP. Therapeutic targeting of p53: All mutants are equal, but some mutants are more equal than others. Nat Rev Clin Oncol. 2018;15(1):13-30.
29. Gomes AS, Ramos H, Inga A, Sousa E, Saraiva L. Structural and Drug Targeting Insights on Mutant p53. Cancers (Basel). 2021;13(13):3344.
30. Joerger AC, Fersht AR. The tumor suppressor p53: From structures to drug discovery. Cold Spring Harb Perspect Biol. 2010;2(6):a000919.
31. Cho Y, Gorina S, Jeffrey PD, Pavletich NP. Crystal structure of a p53 tumor suppressor-DNA complex: Understanding tumorigenic mutations. Science. 1994;265(5170):346-355.
32. Beckerman R, Prives C. Transcriptional regulation by p53. Cold Spring Harb Perspect Biol. 2010;2(8):a000935.
33. el-Deiry WS, Kern SE, Pietenpol JA, Kinzler KW, Vogelstein B. Definition of a consensus binding site for p53. Nat Genet. 1992;1(1):45-49.
34. Vousden KH, Prives C. Blinded by the Light: The Growing Complexity of p53. Cell. 2009;137(3):413-431.
35. Momand J, Zambetti GP, Olson DC, George D, Levine AJ. The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation. Cell. 1992;69(7):1237-1245.
36. Fang S, Jensen JP, Ludwig RL, Vousden KH, Weissman AM. Mdm2 is a RING finger-dependent ubiquitin protein ligase for itself and p53. J Biol Chem. 2000;275(12):8945-8951.
37. Kato S, Han SY, Liu W, Otsuka K, Shibata H, Kanamaru R, et al. Understanding the function-structure and function-mutation relationships of p53 tumor suppressor protein by high-resolution missense mutation analysis. Proc Natl Acad Sci U S A. 2003;100(14):8424-8429.
38. Escoll M, Gargini R, Cuadrado A, Anton IM, Wandosell F. Mutant p53 oncogenic functions in cancer stem cells are regulated by WIP through YAP/TAZ. Oncogene. 2017;36(25):3515-3527.
39. Yue X, Zhang C, Zhao Y, Liu J, Lin AW, Tan VM, et al. Gain-of-function mutant p53 activates small GTPase Rac1 through SUMOylation to promote tumor progression. Genes Dev. 2017;31(16):1641-1654.
40. Haupt Y, Maya R, Kazaz A, Oren M. Mdm2 promotes the rapid degradation of p53. Nature. 1997;387(6630):296-299.
41. Midgley CA, Lane DP. p53 protein stability in tumour cells is not determined by mutation but is dependent on Mdm2 binding. Oncogene. 1997;15(10):1179-1189.
42. Wiech M, Olszewski MB, Tracz-Gaszewska Z, Wawrzynow B, Zylicz M, Zylicz A. Molecular mechanism of mutant p53 stabilization: The role of HSP70 and MDM2. PLoS One. 2012;7(12):e51426.
43. Baugh EH, Ke H, Levine AJ, Bonneau RA, Chan CS. Why are there hotspot mutations in the TP53 gene in human cancers? Cell Death Differ. 2018;25(1):154-160.
44. Yu X, Vazquez A, Levine AJ, Carpizo DR. Allele-specific p53 mutant reactivation. Cancer Cell. 2012;21(5):614-625.
45. Oren M, Rotter V. Mutant p53 gain-of-function in cancer. Cold Spring Harb Perspect Biol. 2010;2(2):a001107.
46. Levine AJ. P53 and The Immune Response: 40 Years of Exploration-A Plan for the Future. Int J Mol Sci. 2020;21(2):541.
47. Wu M, Ye H, Tang Z, Shao C, Lu G, Chen B, et al. p53 dynamics orchestrates with binding affinity to target genes for cell fate decision. Cell Death Dis. 2017;8(10):e3130.
48. Lang GA, Iwakuma T, Suh YA, Liu G, Rao VA, Parant JM, et al. Gain of function of a p53 hot spot mutation in a mouse model of Li-Fraumeni syndrome. Cell. 2004;119(6):861-872.
49. Olive KP, Tuveson DA, Ruhe ZC, Yin B, Willis NA, Bronson RT, et al. Mutant p53 gain of function in two mouse models of Li-Fraumeni syndrome. Cell. 2004;119(6):847-860.
50. Lavigueur A, Maltby V, Mock D, Rossant J, Pawson T, Bernstein A. High incidence of lung, bone, and lymphoid tumors in transgenic mice overexpressing mutant alleles of the p53 oncogene. Mol Cell Biol. 1989;9(9):3982-3991.
51. Dittmer D, Pati S, Zambetti G, Chu S, Teresky AK, Moore M, et al. Gain of function mutations in p53. Nat Genet. 1993;4(1):42-46.
52. Kern SE, Pietenpol JA, Thiagalingam S, Seymour A, Kinzler KW, Vogelstein B. Oncogenic forms of p53 inhibit p53-regulated gene expression. Science. 1992;256(5058):827-830.
53. Shaulian E, Zauberman A, Ginsberg D, Oren M. Identification of a minimal transforming domain of p53: Negative dominance through abrogation of sequence-specific DNA binding. Mol Cell Biol. 1992;12(12):5581-5592.
54. Milner J, Medcalf EA. Cotranslation of activated mutant p53 with wild type drives the wild-type p53 protein into the mutant conformation. Cell. 1991;65(5):765-774.
55. Sun Y, Dong Z, Nakamura K, Colburn NH. Dosage-dependent dominance over wild-type p53 of a mutant p53 isolated from nasopharyngeal carcinoma. Faseb J. 1993;7(10):944-950.
56. Michalovitz D, Halevy O, Oren M. Conditional inhibition of transformation and of cell proliferation by a temperature-sensitive mutant of p53. Cell. 1990;62(4):671-680.
57. Brachmann RK, Yu K, Eby Y, Pavletich NP, Boeke JD. Genetic selection of intragenic suppressor mutations that

reverse the effect of common p53 cancer mutations. Embo J. 1998;17(7):1847-1859.
58. Hupp TR, Meek DW, Midgley CA, Lane DP. Activation of the cryptic DNA binding function of mutant forms of p53. Nucleic Acids Res. 1993;21(14):3167-3174.
59. Selivanova G, Iotsova V, Okan I, Fritsche M, Ström M, Groner B, et al. Restoration of the growth suppression function of mutant p53 by a synthetic peptide derived from the p53 C-terminal domain. Nat Med. 1997;3(6):632-638.
60. Hupp TR, Sparks A, Lane DP. Small peptides activate the latent sequence-specific DNA binding function of p53. Cell. 1995;83(2):237-245.
61. Sabapathy K, Lane DP. Therapeutic targeting of p53: All mutants are equal, but some mutants are more equal than others. Nature Reviews Clinical Oncology. 2018;15(1):13-30.
62. Wang Q, Fan S, Eastman A, Worland PJ, Sausville EA, O'Connor PM. UCN-01: A potent abrogator of G2 checkpoint function in cancer cells with disrupted p53. J Natl Cancer Inst. 1996;88(14):956-965.
63. Heise C, Sampson-Johannes A, Williams A, McCormick F, Von Hoff DD, Kirn DH. ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumoral efficacy that can be augmented by standard chemotherapeutic agents. Nat Med. 1997;3(6):639-645.
64. Foster BA, Coffey HA, Morin MJ, Rastinejad F. Pharmacological rescue of mutant p53 conformation and function. Science. 1999;286(5449):2507-2510.
65. Issaeva N, Friedler A, Bozko P, Wiman KG, Fersht AR, Selivanova G. Rescue of mutants of the tumor suppressor p53 in cancer cells by a designed peptide. Proc Natl Acad Sci U S A. 2003;100(23):13303-13307.
66. Zhang C, Liu J, Xu D, Zhang T, Hu W, Feng Z. Gain-of-function mutant p53 in cancer progression and therapy. J Mol Cell Biol. 2020;12(9):674-687.
67. Zhang Q, Bykov VJN, Wiman KG, Zawacka-Pankau J. APR-246 reactivates mutant p53 by targeting cysteines 124 and 277. Cell Death Dis. 2018;9(5):439.
68. Miller WH Jr., Schipper HM, Lee JS, Singer J, Waxman S. Mechanisms of action of arsenic trioxide. Cancer Res. 2002;62(14):3893-3903.
69. Yedjou C, Tchounwou P, Jenkins J, McMurray R. Basic mechanisms of arsenic trioxide (ATO)-induced apoptosis in human leukemia (HL-60) cells. J Hematol Oncol. 2010;3:28.
70. Chen S, Wu JL, Liang Y, Tang YG, Song HX, Wu LL, et al. Arsenic Trioxide Rescues Structural p53 Mutations through a Cryptic Allosteric Site. Cancer Cell. 2021;39(2):225-239. e8.
71. Song H, Wu J, Tang Y, Dai Y, Xiang X, Li Y, et al. Diverse rescue potencies of p53 mutations to ATO are predetermined by intrinsic mutational properties. Sci Transl Med. 2023;15(690):eabn9155.
72. Butler JS, Loh SN. Structure, function, and aggregation of the zinc-free form of the p53 DNA binding domain. Biochemistry. 2003;42(8):2396-2403.
73. Liu J, Zhang C, Hu W, Feng Z. Tumor suppressor p53 and metabolism. J Mol Cell Biol. 2019;11(4):284-292.
74. Lau HCH, Yu J. Gut microbiome alters functions of mutant p53 to promote tumorigenesis. Signal Transduct Target Ther. 2020;5(1):232.
75. Li T, Kon N, Jiang L, Tan M, Ludwig T, Zhao Y, et al. Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. Cell. 2012;149(6):1269-1283.
76. Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, et al. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015;520(7545):57-62.
77. Heltberg MS, Lucchetti A, Hsieh FS, Minh Nguyen DP, Chen SH, Jensen MH. Enhanced DNA repair through droplet formation and p53 oscillations. Cell. 2022;185(23):4394-4408. e10.
78. Lane DP. Cancer. p53, guardian of the genome. Nature.1992;358(6381):15-16.
79. Hernández Borrero LJ, El-Deiry WS. Tumor suppressor p53: Biology, signaling pathways, and therapeutic targeting. Biochim Biophys Acta Rev Cancer. 2021;1876(1):188556.
80. Liu Y, Gu W. The complexity of p53-mediated metabolic regulation in tumor suppression. Semin Cancer Biol. 2021;85:4-32.
81. Muller PA, Vousden KH. Mutant p53 in cancer: New functions and therapeutic opportunities. Cancer Cell. 2014;25(3):304-317.
82. Grochola LF, Zeron-Medina J, Mériaux S, Bond GL. Single-nucleotide polymorphisms in the p53 signaling pathway. Cold Spring Harb Perspect Biol. 2010;2(5):a001032.
83. Saldaña-Meyer R, Recillas-Targa F. Transcriptional and epigenetic regulation of the p53 tumor suppressor gene. Epigenetics. 2011;6(9):1068-1077.
84. Vieler M, Sanyal S. p53 Isoforms and Their Implications in Cancer. Cancers (Basel). 2018;10(9):288.
85. Walerych D, Kudla G, Gutkowska M, Wawrzynow B, Muller L, King FW, et al. Hsp90 chaperones wild-type p53 tumor suppressor protein. J Biol Chem. 2004;279(47):48836-48845.
86. Liang SH, Clarke MF. Regulation of p53 localization. Eur J Biochem. 2001;268(10):2779-2783.
87. Kwon SK, Saindane M, Baek KH. p53 stability is regulated by diverse deubiquitinating enzymes. Biochim Biophys Acta Rev Cancer. 2017;1868(2):404-411.
88. Kruse JP, Gu W. Modes of p53 regulation. Cell. 2009;137(4):609-622.
89. Bode AM, Dong Z. Post-translational modification of p53 in tumorigenesis. Nat Rev Cancer. 2004;4(10):793-805.
90. Dai C, Gu W. p53 post-translational modification: Deregulated in tumorigenesis. Trends Mol Med. 2010;16(11):528-536.
91. DeHart CJ, Chahal JS, Flint SJ, Perlman DH. Extensive post-translational modification of active and inactivated forms of endogenous p53. Mol Cell Proteomics. 2014;13(1):1-17.
92. Gu B, Zhu WG. Surf the post-translational modification network of p53 regulation. Int J Biol Sci. 2012;8(5):672-684.
93. Thompson T, Tovar C, Yang H, Carvajal D, Binh TV, Xu Q, et al. Phosphorylation of p53 on key serines is dispensable for transcriptional activation and apoptosis. The Journal of biological chemistry. 2004;279(51):53015-53022.
94. Sakaguchi K, Herrera JE, Saito S, Miki T, Bustin M, Vassilev A, et al. DNA damage activates p53 through a phosphorylation-acetylation cascade. Genes Dev. 1998;12(18):2831-2841.
95. Loughery J, Cox M, Smith LM, Meek DW. Critical role for p53-serine 15 phosphorylation in stimulating transactivation at p53-responsive promoters. Nucleic Acids Res. 2014;42(12):7666-7680.

96. Shieh SY, Ikeda M, Taya Y, Prives C. DNA damage-induced phosphorylation of p53 alleviates inhibition by MDM2. Cell. 1997;91(3):325-334.
97. Chehab NH, Malikzay A, Stavridi ES, Halazonetis TD. Phosphorylation of Ser-20 mediates stabilization of human p53 in response to DNA damage. Proc Natl Acad Sci U S A. 1999;96(24):13777-13782.
98. Hofmann TG, Möller A, Sirma H, Zentgraf H, Taya Y, Dröge W, et al. Regulation of p53 activity by its interaction with homeodomain-interacting protein kinase-2. Nature cell biology. 2002;4(1):1-10.
99. D'Orazi G, Cecchinelli B, Bruno T, Manni I, Higashimoto Y, Saito S, et al. Homeodomain-interacting protein kinase-2 phosphorylates p53 at Ser 46 and mediates apoptosis. Nature cell biology. 2002;4(1):11-19.
100. Wang F, Marshall CB, Ikura M. Transcriptional/epigenetic regulator CBP/p300 in tumorigenesis: Structural and functional versatility in target recognition. Cell Mol Life Sci. 2013;70(21):3989-4008.
101. Karamouzis MV, Konstantinopoulos PA, Papavassiliou AG. Roles of CREB-binding protein (CBP)/p300 in respiratory epithelium tumorigenesis. Cell Res. 2007;17(4):324-332.
102. Gu W, Luo J, Brooks CL, Nikolaev AY, Li M. Dynamics of the p53 acetylation pathway. Novartis Found Symp. 2004;259:197-205.
103. Avantaggiati ML, Ogryzko V, Gardner K, Giordano A, Levine AS, Kelly K. Recruitment of p300/CBP in p53-dependent signal pathways. Cell. 1997;89(7):1175-1184.
104. Lill NL, Grossman SR, Ginsberg D, DeCaprio J, Livingston DM. Binding and modulation of p53 by p300/CBP coactivators. Nature. 1997;387(6635):823-827.
105. Trigiante G, Lu X. ASPP [corrected] and cancer. Nat Rev Cancer. 2006;6(3):217-226.
106. Gillotin S, Lu X. The ASPP proteins complex and cooperate with p300 to modulate the transcriptional activity of p53. FEBS Lett. 2011;585(12):1778-1782.
107. Meek DW, Anderson CW. Posttranslational modification of p53: Cooperative integrators of function. Cold Spring Harb Perspect Biol. 2009;1(6):a000950.
108. Ghosh R, Kaypee S, Shasmal M, Kundu TK, Roy S, Sengupta J. Tumor Suppressor p53-Mediated Structural Reorganization of the Transcriptional Coactivator p300. Biochemistry. 2019;58(32):3434-3443.
109. Verdone L, Agricola E, Caserta M, Di Mauro E. Histone acetylation in gene regulation. Brief Funct Genomic Proteomic. 2006;5(3):209-221.
110. DesJarlais R, Tummino PJ. Role of Histone-Modifying Enzymes and Their Complexes in Regulation of Chromatin Biology. Biochemistry. 2016;55(11):1584-1599.
111. Sterner R, Vidali G, Allfrey VG. Studies of acetylation and deacetylation in high mobility group proteins. Identification of the sites of acetylation in HMG-1. J Biol Chem. 1979;254(22):11577-11583.
112. L'Hernault SW, Rosenbaum JL. Chlamydomonas alpha-tubulin is posttranslationally modified in the flagella during flagellar assembly. J Cell Biol. 1983;97(1):258-263.
113. Gu W, Shi XL, Roeder RG. Synergistic activation of transcription by CBP and p53. Nature. 1997;387(6635):819-823.
114. Verdin E, Ott M. 50 years of protein acetylation: From gene regulation to epigenetics, metabolism and beyond. Nat Rev Mol Cell Biol. 2015;16(4):258-264.
115. Narita T, Weinert BT, Choudhary C. Functions and mechanisms of non-histone protein acetylation. Nat Rev Mol Cell Biol. 2019;20(3):156-174.
116. Gu W, Roeder RG. Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell. 1997;90(4):595-606.
117. Chiarugi V, Cinelli M, Magnelli L. Acetylation and phosphorylation of the carboxy-terminal domain of p53: Regulative significance. Oncol Res. 1998;10(2):55-57.
118. Wang Y, Chen Y, Chen Q, Zhang X, Wang H, Wang Z, et al. The role of acetylation sites in the regulation of p53 activity. Mol Biol Rep. 2020;47(1):381-391.
119. Liang L, Wang H, Shi H, Li Z, Yao H, Bu Z, et al. A Designed Peptide Targets Two Types of Modifications of p53 with Anticancer Activity. Cell Chem Biol. 2018;25(6):761-774. e5.
120. Wang B, Li D, Filkowski J, Rodriguez-Juarez R, Storozynsky Q, Malach M, et al. A dual role of miR-22 modulated by RelA/p65 in resensitizing fulvestrant-resistant breast cancer cells to fulvestrant by targeting FOXP1 and HDAC4 and constitutive acetylation of p53 at Lys382. Oncogenesis. 2018;7(7):54.
121. Li M, Luo J, Brooks CL, Gu W. Acetylation of p53 inhibits its ubiquitination by Mdm2. J Biol Chem. 2002;277(52):50607-50611.
122. Liu Y, Tavana O, Gu W. p53 modifications: Exquisite decorations of the powerful guardian. J Mol Cell Biol. 2019;11(7):564-577.
123. Lee CW, Sørensen TS, Shikama N, La Thangue NB. Functional interplay between p53 and E2F through co-activator p300. Oncogene. 1998;16(21):2695-2710.
124. Grossman SR, Deato ME, Brignone C, Chan HM, Kung AL, Tagami H, et al. Polyubiquitination of p53 by a ubiquitin ligase activity of p300. Science. 2003;300(5617):342-344.
125. Hutvágner G, McLachlan J, Pasquinelli AE, Bálint E, Tuschl T, Zamore PD. A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. Science. 2001;293(5531):834-838.
126. Bernstein E, Caudy AA, Hammond SM, Hannon GJ. Role for a bidentate ribonuclease in the initiation step of RNA interference. Nature. 2001;409(6818):363-366.
127. Yang X, Wang X, Li Z, Duan S, Li H, Jin J, et al. An unexpected role for Dicer as a reader of the unacetylated DNA binding domain of p53 in transcriptional regulation. Sci Adv. 2021;7(44):eabi6684.
128. Meek DW. Post-translational modification of p53. Semin Cancer Biol. 1994;5(3):203-210.
129. Knights CD, Catania J, Di Giovanni S, Muratoglu S, Perez R, Swartzbeck A, et al. Distinct p53 acetylation cassettes differentially influence gene-expression patterns and cell fate. J Cell Biol. 2006;173(4):533-544.
130. Sykes SM, Stanek TJ, Frank A, Murphy ME, McMahon SB. Acetylation of the DNA binding domain regulates transcription-independent apoptosis by p53. J Biol Chem. 2009;284(30):20197-20205.
131. Juang YC, Landry MC, Sanches M, Vittal V, Leung CC, Ceccarelli DF, et al. OTUB1 co-opts Lys48-linked

ubiquitin recognition to suppress E2 enzyme function. Mol Cell. 2012;45(3):384-397.
132. Nagasaka M, Miyajima C, Aoki H, Aoyama M, Morishita D, Inoue Y, et al. Insights into Regulators of p53 Acetylation. Cells. 2022;11(23):3825.
133. Zhang J, Shen L, Sun LQ. The regulation of radiosensitivity by p53 and its acetylation. Cancer Lett. 2015;363(2):108-118.
134. He Y, Gao M, Cao Y, Tang H, Liu S, Tao Y. Nuclear localization of metabolic enzymes in immunity and metastasis. Biochim Biophys Acta Rev Cancer. 2017;1868(2):359-371.
135. Jansson M, Durant ST, Cho EC, Sheahan S, Edelmann M, Kessler B, et al. Arginine methylation regulates the p53 response. Nat Cell Biol. 2008;10(12):1431-1439.
136. Campaner S, Spreafico F, Burgold T, Doni M, Rosato U, Amati B, et al. The methyltransferase Set7/9 (Setd7) is dispensable for the p53-mediated DNA damage response in vivo. Mol Cell. 2011;43(4):681-688.
137. Abaev-Schneiderman E, Admoni-Elisha L, Levy D. SETD3 is a positive regulator of DNA-damage-induced apoptosis. Cell Death Dis. 2019;10(2):74.
138. Chuikov S, Kurash JK, Wilson JR, Xiao B, Justin N, Ivanov GS, et al. Regulation of p53 activity through lysine methylation. Nature. 2004;432(7015):353-360.
139. Raposo AE, Piller SC. Protein arginine methylation: An emerging regulator of the cell cycle. Cell Div. 2018;13:3.
140. Hill SY, Rompala G, Homanics GE, Zezza N. Cross-generational effects of alcohol dependence in humans on HRAS and TP53 methylation in offspring. Epigenomics. 2017;9(9):1189-1203.
141. Li Y, Chitnis N, Nakagawa H, Kita Y, Natsugoe S, Yang Y, et al. PRMT5 is required for lymphomagenesis triggered by multiple oncogenic drivers. Cancer Discov. 2015;5(3):288-303.
142. Berger SL. Out of the jaws of death: PRMT5 steers p53. Nat Cell Biol. 2008;10(12):1389-1390.
143. Sims RJ 3rd, Reinberg D. Is there a code embedded in proteins that is based on post-translational modifications? Nat Rev Mol Cell Biol. 2008;9(10):815-820.
144. Huang J, Perez-Burgos L, Placek BJ, Sengupta R, Richter M, Dorsey JA, et al. Repression of p53 activity by Smyd2-mediated methylation. Nature. 2006;444(7119):629-632.
145. Chuikov S, Kurash JK, Wilson JR, Xiao B, Justin N, Ivanov GS, et al. Regulation of p53 activity through lysine methylation. Nature. 2004;432(7015):353-360.
146. Shi X, Kachirskaia I, Yamaguchi H, West LE, Wen H, Wang EW, et al. Modulation of p53 function by SET8-mediated methylation at lysine 382. Mol Cell. 2007;27(4):636-646.
147. Huang J, Sengupta R, Espejo AB, Lee MG, Dorsey JA, Richter M, et al. p53 is regulated by the lysine demethylase LSD1. Nature. 2007;449(7158):105-108.
148. Carr SM, Poppy Roworth A, Chan C, La Thangue NB. Post-translational control of transcription factors: Methylation ranks highly. Febs j. 2015;282(23):4450-4465.
149. Garner E, Raj K. Protective mechanisms of p53-p21-pRb proteins against DNA damage-induced cell death. Cell Cycle. 2008;7(3):277-282.
150. Kung CP, Khaku S, Jennis M, Zhou Y, Murphy ME. Identification of TRIML2, a novel p53 target, that enhances p53 SUMOylation and regulates the transactivation of proapoptotic genes. Mol Cancer Res. 2015;13(2):250-262.
151. Stehmeier P, Muller S. Regulation of p53 family members by the ubiquitin-like SUMO system. DNA Repair (Amst). 2009;8(4):491-498.
152. Kahyo T, Nishida T, Yasuda H. Involvement of PIAS1 in the sumoylation of tumor suppressor p53. Mol Cell. 2001;8(3):713-718.
153. Santiago A, Li D, Zhao LY, Godsey A, Liao D. p53 SUMOylation promotes its nuclear export by facilitating its release from the nuclear export receptor CRM1. Mol Biol Cell. 2013;24(17):2739-2752.
154. Mihara M, Erster S, Zaika A, Petrenko O, Chittenden T, Pancoska P, et al. p53 has a direct apoptogenic role at the mitochondria. Mol Cell. 2003;11(3):577-590.
155. Heo KS, Berk BC, Abe J. Disturbed Flow-Induced Endothelial Proatherogenic Signaling Via Regulating Post-Translational Modifications and Epigenetic Events. Antioxid Redox Signal. 2016;25(7):435-450.
156. Ashikari D, Takayama K, Tanaka T, Suzuki Y, Obinata D, Fujimura T, et al. Androgen induces G3BP2 and SUMO-mediated p53 nuclear export in prostate cancer. Oncogene. 2017;36(45):6272-6281.
157. Pickart CM. Mechanisms underlying ubiquitination. Annu Rev Biochem. 2001;70:503-533.
158. Senft D, Qi J, Ronai ZA. Ubiquitin ligases in oncogenic transformation and cancer therapy. Nat Rev Cancer. 2018;18(2):69-88.
159. Mukhopadhyay D, Riezman H. Proteasome-independent functions of ubiquitin in endocytosis and signaling. Science. 2007;315(5809):201-205.
160. Scheffner M, Huibregtse JM, Vierstra RD, Howley PM. The HPV-16 E6 and E6-AP complex functions as a ubiquitin-protein ligase in the ubiquitination of p53. Cell. 1993;75(3):495-505.
161. Rodriguez MS, Desterro JM, Lain S, Lane DP, Hay RT. Multiple C-terminal lysine residues target p53 for ubiquitin-proteasome-mediated degradation. Mol Cell Biol. 2000;20(22):8458-8467.
162. Li M, Brooks CL, Wu-Baer F, Chen D, Baer R, Gu W. Mono- versus polyubiquitination: Differential control of p53 fate by Mdm2. Science. 2003;302(5652):1972-1975.
163. Green DR, Kroemer G. Cytoplasmic functions of the tumour suppressor p53. Nature. 2009;458(7242):1127-1130.
164. Brooks CL, Gu W. p53 ubiquitination: Mdm2 and beyond. Mol Cell. 2006;21(3):307-315.
165. Moyer SM, Larsson CA, Lozano G. Mdm proteins: Critical regulators of embry ogenesis and homeostasis. J Mol Cell Biol. 2017;9(1):16-25.
166. Rong X, Rao J, Li D, Jing Q, Lu Y, Ji Y. TRIM69 inhibits cataractogenesis by negatively regulating p53. Redox Biol. 2019;22:101157.
167. Zhou Z, Ji Z, Wang Y, Li J, Cao H, Zhu HH, et al. TRIM59 is up-regulated in gastric tumors, promoting ubiquitination and degradation of p53. Gastroenterology. 2014;147(5):1043-1054.
168. Esser C, Scheffner M, Höhfeld J. The chaperone-associated ubiquitin ligase CHIP is able to target p53 for proteasomal degradation. J Biol Chem. 2005;280(29):27443-27448.
169. Dornan D, Wertz I, Shimizu H, Arnott D, Frantz GD, Dowd P, et al. The ubiquitin ligase COP1 is a critical negative regulator of p53. Nature. 2004;429(6987):86-92.
170. Carter S, Vousden KH. p53-Ubl fusions as models of ubiquitination, sumoylation and neddylation of p53. Cell Cycle. 2008;7(16):2519-2528.

171. Rabut G, Peter M. Function and regulation of protein neddylation. 'Protein modifications: Beyond the usual suspects' review series. EMBO Rep. 2008;9(10):969-976.
172. Wu SY, Chiang CM. Crosstalk between sumoylation and acetylation regulates p53-dependent chromatin transcription and DNA binding. Embo j. 2009;28(9):1246-1259.
173. Xirodimas DP, Saville MK, Bourdon JC, Hay RT, Lane DP. Mdm2-mediated NEDD8 conjugation of p53 inhibits its transcriptional activity. Cell. 2004;118(1):83-97.
174. Abida WM, Nikolaev A, Zhao W, Zhang W, Gu W. FBXO11 promotes the Neddylation of p53 and inhibits its transcriptional activity. J Biol Chem. 2007;282(3):1797-1804.
175. Yang WH, Kim JE, Nam HW, Ju JW, Kim HS, Kim YS, et al. Modification of p53 with O-linked N-acetylglucosamine regulates p53 activity and stability. Nat Cell Biol. 2006;8(10):1074-1083.
176. Ozcan S, Andrali SS, Cantrell JE. Modulation of transcription factor function by O-GlcNAc modification. Biochim Biophys Acta. 2010;1799(5-6):353-364.
177. Rodriguez J, Herrero A, Li S, Rauch N, Quintanilla A, Wynne K, et al. PHD3 Regulates p53 Protein Stability by Hydroxylating Proline 359. Cell Rep. 2018;24(5):1316-1329.
178. Ko A, Han SY, Choi CH, Cho H, Lee MS, Kim SY, et al. Oncogene-induced senescence mediated by c-Myc requires USP10 dependent deubiquitination and stabilization of p14ARF. Cell Death Differ. 2018;25(6):1050-1062.
179. Jochemsen AG, Shiloh Y. USP10: Friend and foe. Cell. 2010;140(3):308-310.
180. Liu K, Li F, Sun Q, Lin N, Han H, You K, et al. p53 β-hydroxybutyrylation attenuates p53 activity. Cell Death Dis. 2019;10(3):243.
181. Lee SY, Park JH, Jeong S, Kim BY, Kang YK, Xu Y, et al. K120R mutation inactivates p53 by creating an aberrant splice site leading to nonsense-mediated mRNA decay. Oncogene. 2019;38(10):1597-1610.
182. Lahav G, Rosenfeld N, Sigal A, Geva-Zatorsky N, Levine AJ, Elowitz MB, et al. Dynamics of the p53-Mdm2 feedback loop in individual cells. Nat Genet. 2004;36(2):147-150.
183. Leslie PL, Franklin DA, Liu Y, Zhang Y. p53 Regulates the Expression of LRP1 and Apoptosis through a Stress Intensity-Dependent MicroRNA Feedback Loop. Cell Rep. 2018;24(6):1484-1495.
184. Purvis JE, Karhohs KW, Mock C, Batchelor E, Loewer A, Lahav G. p53 dynamics control cell fate. Science. 2012;336(6087):1440-1444.
185. Lowe SW, Bodis S, McClatchey A, Remington L, Ruley HE, Fisher DE, et al. p53 status and the efficacy of cancer therapy in vivo. Science. 1994;266(5186):807-810.
186. Hafner A, Stewart-Ornstein J, Purvis JE, Forrester WC, Bulyk ML, Lahav G. p53 pulses lead to distinct patterns of gene expression albeit similar DNA-binding dynamics. Nat Struct Mol Biol. 2017;24(10):840-847.
187. Pant V, Xiong S, Wasylishen AR, Larsson CA, Aryal NK, Chau G, et al. Transient enhancement of p53 activity protects from radiation-induced gastrointestinal toxicity. Proc Natl Acad Sci U S A. 2019;116(35):17429-17437.
188. Scian MJ, Stagliano KE, Anderson MA, Hassan S, Bowman M, Miles MF, et al. Tumor-derived p53 mutants induce NF-kappaB2 gene expression. Mol Cell Biol. 2005;25(22):10097-10110.
189. Jiménez A, Lu D, Kalocsay M, Berberich MJ, Balbi P, Jambhekar A, et al. Time-series transcriptomics and proteomics reveal alternative modes to decode p53 oscillations. Molecular systems biology. 2022;18(3):e10588.
190. Porter JR, Fisher BE, Batchelor E. p53 Pulses Diversify Target Gene Expression Dynamics in an mRNA Half-Life-Dependent Manner and Delineate Co-regulated Target Gene Subnetworks. Cell Syst. 2016;2(4):272-282.
191. Stewart-Ornstein J, Iwamoto Y, Miller MA, Prytyskach MA, Ferretti S, Holzer P, et al. p53 dynamics vary between tissues and are linked with radiation sensitivity. Nat Commun. 2021;12(1):898.
192. Bourdon JC. p53 isoforms change p53 paradigm. Mol Cell Oncol. 2014;1(4):e969136.
193. Lawrence MS, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature. 2014;505(7484):495-501.
194. Brosh R, Rotter V. When mutants gain new powers: News from the mutant p53 field. Nat Rev Cancer. 2009;9(10):701-713.
195. Kandoth C, McLellan MD, Vandin F, Ye K, Niu B, Lu C, et al. Mutational landscape and significance across 12 major cancer types. Nature. 2013;502(7471):333-339.
196. Zhang Z, Hao R, Guo Q, Zhang S, Wang X. TP53 Mutation Infers a Poor Prognosis and Is Correlated to Immunocytes Infiltration in Breast Cancer. Front Cell Dev Biol. 2021;9:759154.
197. Leroy B, Anderson M, Soussi T. TP53 mutations in human cancer: Database reassessment and prospects for the next decade. Hum Mutat. 2014;35(6):672-688.
198. Leroy B, Ballinger ML, Baran-Marszak F, Bond GL, Braithwaite A, Concin N, et al. Recommended Guidelines for Validation, Quality Control, and Reporting of TP53 Variants in Clinical Practice. Cancer Res. 2017;77(6):1250-1260.
199. Stiewe T, Haran TE. How mutations shape p53 interactions with the genome to promote tumorigenesis and drug resistance. Drug Resist Updat. 2018;38:27-43.
200. Chiang YT, Chien YC, Lin YH, Wu HH, Lee DF, Yu YL. The Function of the Mutant p53-R175H in Cancer. Cancers (Basel). 2021;13(16):4088.
201. Chen X, Zhang T, Su W, Dou Z, Zhao D, Jin X, et al. Mutant p53 in cancer: From molecular mechanism to therapeutic modulation. Cell Death Dis. 2022;13(11):974.
202. Zhu G, Pan C, Bei JX, Li B, Liang C, Xu Y, et al. Mutant p53 in Cancer Progression and Targeted Therapies. Front Oncol. 2020;10:595187.
203. Shirole NH, Pal D, Kastenhuber ER, Senturk S, Boroda J, Pisterzi P, et al. TP53 exon-6 truncating mutations produce separation of function isoforms with pro-tumorigenic functions. Elife. 2016;5:e17929.
204. Quinn EA, Maciaszek JL, Pinto EM, Phillips AH, Berdy D, Khandwala M, et al. From uncertainty to pathogenicity: Clinical and functional interrogation of a rare TP53 in-frame deletion. Cold Spring Harb Mol Case Stud. 2019;5(4):a003921.
205. Pfeifer GP, Besaratinia A. Mutational spectra of human cancer. Hum Genet. 2009;125(5-6):493-506.
206. Chasov V, Mirgayazova R, Zmievskaya E, Khadiullina R, Valiullina A, Stephenson Clarke J, et al. Key Players in

the Mutant p53 Team: Small Molecules, Gene Editing, Immunotherapy. Front Oncol. 2020;10:1460.
207. Gaiddon C, Lokshin M, Ahn J, Zhang T, Prives C. A subset of tumor-derived mutant forms of p53 down-regulate p63 and p73 through a direct interaction with the p53 core domain. Mol Cell Biol. 2001;21(5):1874-1887.
208. Strano S, Fontemaggi G, Costanzo A, Rizzo MG, Monti O, Baccarini A, et al. Physical interaction with human tumor-derived p53 mutants inhibits p63 activities. J Biol Chem. 2002;277(21):18817-18826.
209. Phang BH, Othman R, Bougeard G, Chia RH, Frebourg T, Tang CL, et al. Amino-terminal p53 mutations lead to expression of apoptosis proficient p47 and prognosticate better survival, but predispose to tumorigenesis. Proc Natl Acad Sci U S A. 2015;112(46):E6349-E6358.
210. Ryan KM, Vousden KH. Characterization of structural p53 mutants which show selective defects in apoptosis but not cell cycle arrest. Mol Cell Biol. 1998;18(7):3692-3698.
211. Liu Q, Yu B, Tian Y, Dan J, Luo Y, Wu X. P53 Mutant p53N236S Regulates Cancer-Associated Fibroblasts Properties Through Stat3 Pathway. Onco Targets Ther. 2020;13:1355-1363.
212. Fischer M, Uxa S, Stanko C, Magin TM, Engeland K. Human papilloma virus E7 oncoprotein abrogates the p53-p21-DREAM pathway. Sci Rep. 2017;7(1):2603.
213. Celegato M, Messa L, Goracci L, Mercorelli B, Bertagnin C, Spyrakis F, et al. A novel small-molecule inhibitor of the human papillomavirus E6-p53 interaction that reactivates p53 function and blocks cancer cells growth. Cancer Lett. 2020;470:115-125.
214. Soragni A, Janzen DM, Johnson LM, Lindgren AG, Thai-Quynh Nguyen A, Tiourin E, et al. A Designed Inhibitor of p53 Aggregation Rescues p53 Tumor Suppression in Ovarian Carcinomas. Cancer Cell. 2016;29(1):90-103.
215. Maan M, Pati U. CHIP promotes autophagy-mediated degradation of aggregating mutant p53 in hypoxic conditions. Febs j. 2018;285(17):3197-3214.
216. Costa DC, de Oliveira GA, Cino EA, Soares IN, Rangel LP, Silva JL. Aggregation and Prion-Like Properties of Misfolded Tumor Suppressors: Is Cancer a Prion Disease? Cold Spring Harb Perspect Biol. 2016;8(10):a023614.
217. Bykov VJN, Eriksson SE, Bianchi J, Wiman KG. Targeting mutant p53 for efficient cancer therapy. Nat Rev Cancer. 2018;18(2):89-102.
218. Hollstein M, Sidransky D, Vogelstein B, Harris CC. p53 mutations in human cancers. Science. 1991;253(5015):49-53.
219. Kucab JE, Phillips DH, Arlt VM. Linking environmental carcinogen exposure to TP53 mutations in human tumours using the human TP53 knock-in (Hupki) mouse model. Febs J. 2010;277(12):2567-2583.
220. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene. 2002;21(48):7435-7451.
221. Petitjean A, Achatz MI, Borresen-Dale AL, Hainaut P, Olivier M. TP53 mutations in human cancers: Functional selection and impact on cancer prognosis and outcomes. Oncogene. 2007;26(15):2157-2165.
222. Resnick MA, Inga A. Functional mutants of the sequence-specific transcription factor p53 and implications for master genes of diversity. Proc Natl Acad Sci U S A. 2003;100(17):9934-999.
223. Freed-Pastor WA, Prives C. Mutant p53: One name, many proteins. Genes Dev. 2012;26(12):1268-1286.
224. Di Agostino S, Strano S, Emiliozzi V, Zerbini V, Mottolese M, Sacchi A, et al. Gain of function of mutant p53: The mutant p53/NF-Y protein complex reveals an aberrant transcriptional mechanism of cell cycle regulation. Cancer Cell. 2006;10(3):191-202.
225. Brosh R, Rotter V. Transcriptional control of the proliferation cluster by the tumor suppressor p53. Mol Biosyst. 2010;6(1):17-29.
226. Di Agostino S, Sorrentino G, Ingallina E, Valenti F, Ferraiuolo M, Bicciato S, et al. YAP enhances the pro-proliferative transcriptional activity of mutant p53 proteins. EMBO Rep. 2016;17(2):188-201.
227. Singh S, Vaughan CA, Frum RA, Grossman SR, Deb S, Palit Deb S. Mutant p53 establishes targetable tumor dependency by promoting unscheduled replication. J Clin Invest. 2017;127(5):1839-1855.
228. Verduci L, Ferraiuolo M, Sacconi A, Ganci F, Vitale J, Colombo T, et al. The oncogenic role of circPVT1 in head and neck squamous cell carcinoma is mediated through the mutant p53/YAP/TEAD transcription-competent complex. Genome Biol. 2017;18(1):237.
229. Wang W, Cheng B, Miao L, Mei Y, Wu M. Mutant p53-R273H gains new function in sustained activation of EGFR signaling via suppressing miR-27a expression. Cell Death Dis. 2013;4(4):e574.
230. Schulz-Heddergott R, Stark N, Edmunds SJ, Li J, Conradi LC, Bohnenberger H, et al. Therapeutic Ablation of Gain-of-Function Mutant p53 in Colorectal Cancer Inhibits Stat3-Mediated Tumor Growth and Invasion. Cancer Cell. 2018;34(2):298-314. e7.
231. Zhu J, Sammons MA, Donahue G, Dou Z, Vedadi M, Getlik M, et al. Gain-of-function p53 mutants co-opt chromatin pathways to drive cancer growth. Nature. 2015;525(7568):206-211.
232. Muller PA, Vousden KH, Norman JC. p53 and its mutants in tumor cell migration and invasion. J Cell Biol. 2011;192(2):209-218.
233. Powell E, Piwnica-Worms D, Piwnica-Worms H. Contribution of p53 to metastasis. Cancer Discov. 2014;4(4):405-414.
234. Zhang C, Liu J, Zhao Y, Yue X, Zhu Y, Wang X, et al. Glutaminase 2 is a novel negative regulator of small GTPase Rac1 and mediates p53 function in suppressing metastasis. Elife. 2016;5:e10727.
235. Dong P, Karaayvaz M, Jia N, Kaneuchi M, Hamada J, Watari H, et al. Mutant p53 gain-of-function induces epithelial-mesenchymal transition through modulation of the miR-130b-ZEB1 axis. Oncogene. 2013;32(27):3286-3295.
236. Kogan-Sakin I, Tabach Y, Buganim Y, Molchadsky A, Solomon H, Madar S, et al. Mutant p53(R175H) upregulates Twist1 expression and promotes epithelial-mesenchymal transition in immortalized prostate cells. Cell Death Differ. 2011;18(2):271-281.
237. Adorno M, Cordenonsi M, Montagner M, Dupont S, Wong C, Hann B, et al. A Mutant-p53/Smad complex opposes p63 to empower TGFbeta-induced metastasis. Cell. 2009;137(1):87-98.

238. Muller PA, Caswell PT, Doyle B, Iwanicki MP, Tan EH, Karim S, et al. Mutant p53 drives invasion by promoting integrin recycling. Cell. 2009;139(7):1327-1341.
239. Muller PA, Trinidad AG, Timpson P, Morton JP, Zanivan S, van den Berghe PV, et al. Mutant p53 enhances MET trafficking and signalling to drive cell scattering and invasion. Oncogene. 2013;32(10):1252-1265.
240. Novo D, Heath N, Mitchell L, Caligiuri G, MacFarlane A, Reijmer D, et al. Mutant p53s generate pro-invasive niches by influencing exosome podocalyxin levels. Nat Commun. 2018;9(1):5069.
241. Weissmueller S, Manchado E, Saborowski M, M JPt, Wagenblast E, Davis CA, et al. Mutant p53 drives pancreatic cancer metastasis through cell-autonomous PDGF receptor β signaling. Cell. 2014;157(2):382-394.
242. Pourebrahim R, Zhang Y, Liu B, Gao R, Xiong S, Lin PP, et al. Integrative genome analysis of somatic p53 mutant osteosarcomas identifies Ets2-dependent regulation of small nucleolar RNAs by mutant p53 protein. Genes Dev. 2017;31(18):1847-1857.
243. Xiong S, Tu H, Kollareddy M, Pant V, Li Q, Zhang Y, et al. Pla2g16 phospholipase mediates gain-of-function activities of mutant p53. Proceedings of the National Academy of Sciences. 2014;111(30):11145-11150.
244. Hanel W, Moll UM. Links between mutant p53 and genomic instability. J Cell Biochem. 2012;113(2):433-439.
245. Gualberto A, Aldape K, Kozakiewicz K, Tlsty TD. An oncogenic form of p53 confers a dominant, gain-of-function phenotype that disrupts spindle checkpoint control. Proc Natl Acad Sci U S A. 1998;95(9):5166-5171.
246. Murphy KL, Dennis AP, Rosen JM. A gain of function p53 mutant promotes both genomic instability and cell survival in a novel p53-null mammary epithelial cell model. Faseb j. 2000;14(14):2291-2302.
247. Hingorani SR, Wang L, Multani AS, Combs C, Deramaudt TB, Hruban RH, et al. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. Cancer Cell. 2005;7(5):469-483.
248. Song H, Hollstein M, Xu Y. p53 gain-of-function cancer mutants induce genetic instability by inactivating ATM. Nat Cell Biol. 2007;9(5):573-580.
249. Valenti F, Ganci F, Fontemaggi G, Sacconi A, Strano S, Blandino G, et al. Gain of function mutant p53 proteins cooperate with E2F4 to transcriptionally downregulate RAD17 and BRCA1 gene expression. Oncotarget. 2015;6(8):5547-5566.
250. Polotskaia A, Xiao G, Reynoso K, Martin C, Qiu WG, Hendrickson RC, et al. Proteome-wide analysis of mutant p53 targets in breast cancer identifies new levels of gain-of-function that influence PARP, PCNA, and MCM4. Proc Natl Acad Sci U S A. 2015;112(11):e1220-e1229.
251. Tomasini R, Tsuchihara K, Tsuda C, Lau SK, Wilhelm M, Rufini A, et al. TAp73 regulates the spindle assembly checkpoint by modulating BubR1 activity. Proc Natl Acad Sci U S A. 2009;106(3):797-802.
252. Mackay HL, Moore D, Hall C, Birkbak NJ, Jamal-Hanjani M, Karim SA, et al. Genomic instability in mutant p53 cancer cells upon entotic engulfment. Nat Commun. 2018;9(1):3070.
253. Shetzer Y, Molchadsky A, Rotter V. Oncogenic Mutant p53 Gain of Function Nourishes the Vicious Cycle of Tumor Development and Cancer Stem-Cell Formation. Cold Spring Harb Perspect Med. 2016;6(10):a026203.
254. Shetzer Y, Kagan S, Koifman G, Sarig R, Kogan-Sakin I, Charni M, et al. The onset of p53 loss of heterozygosity is differentially induced in various stem cell types and may involve the loss of either allele. Cell Death Differ. 2014;21(9):1419-1431.
255. Wang Y, Yang J, Zheng H, Tomasek GJ, Zhang P, McKeever PE, et al. Expression of mutant p53 proteins implicates a lineage relationship between neural stem cells and malignant astrocytic glioma in a murine model. Cancer Cell. 2009;15(6):514-526.
256. Solomon H, Dinowitz N, Pateras IS, Cooks T, Shetzer Y, Molchadsky A, et al. Mutant p53 gain of function underlies high expression levels of colorectal cancer stem cells markers. Oncogene. 2018;37(12):1669-1684.
257. Loizou E, Banito A, Livshits G, Ho YJ, Koche RP, Sánchez-Rivera FJ, et al. A Gain-of-Function p53-Mutant Oncogene Promotes Cell Fate Plasticity and Myeloid Leukemia through the Pluripotency Factor FOXH1. Cancer Discov. 2019;9(7):962-979.
258. Labuschagne CF, Zani F, Vousden KH. Control of metabolism by p53 - Cancer and beyond. Biochim Biophys Acta Rev Cancer. 2018;1870(1):32-42.
259. Matoba S, Kang JG, Patino WD, Wragg A, Boehm M, Gavrilova O, et al. p53 regulates mitochondrial respiration. Science. 2006;312(5780):1650-1653.
260. Zhang C, Liu J, Liang Y, Wu R, Zhao Y, Hong X, et al. Tumour-associated mutant p53 drives the Warburg effect. Nat Commun. 2013;4:2935.
261. Mathupala SP, Heese C, Pedersen PL. Glucose catabolism in cancer cells. The type II hexokinase promoter contains functionally active response elements for the tumor suppressor p53. J Biol Chem. 1997;272(36):22776-22780.
262. Dando I, Cordani M, Donadelli M. Mutant p53 and mTOR/PKM2 regulation in cancer cells. IUBMB Life. 2016;68(9):722-726.
263. Freed-Pastor WA, Mizuno H, Zhao X, Langerød A, Moon SH, Rodriguez-Barrueco R, et al. Mutant p53 disrupts mammary tissue architecture via the mevalonate pathway. Cell. 2012;148(1-2):244-258.
264. Kollareddy M, Dimitrova E, Vallabhaneni KC, Chan A, Le T, Chauhan KM, et al. Regulation of nucleotide metabolism by mutant p53 contributes to its gain-of-function activities. Nat Commun. 2015;6:7389.
265. Basu S, Gnanapradeepan K, Barnoud T, Kung CP, Tavecchio M, Scott J, et al. Mutant p53 controls tumor metabolism and metastasis by regulating PGC-1α. Genes Dev. 2018;32(3-4):230-243.
266. Zhao Y, Wu L, Yue X, Zhang C, Wang J, Li J, et al. A polymorphism in the tumor suppressor p53 affects aging and longevity in mouse models. Elife. 2018;7:e34701.
267. Barnoud T, Parris JLD, Murphy ME. Common genetic variants in the TP53 pathway and their impact on cancer. J Mol Cell Biol. 2019;11(7):578-585.
268. Mizuno H, Spike BT, Wahl GM, Levine AJ. Inactivation of p53 in breast cancers correlates with stem cell transcriptional signatures. Proc Natl Acad Sci U S A. 2010;107(52):22745-22750.
269. Hong H, Takahashi K, Ichisaka T, Aoi T, Kanagawa O, Nakagawa M, et al. Suppression of induced pluripo-

tent stem cell generation by the p53-p21 pathway. Nature. 2009;460(7259):1132-1135.
270. Kawamura T, Suzuki J, Wang YV, Menendez S, Morera LB, Raya A, et al. Linking the p53 tumour suppressor pathway to somatic cell reprogramming. Nature. 2009;460(7259):1140-1144.
271. Li H, Collado M, Villasante A, Strati K, Ortega S, Cañamero M, et al. The Ink4/Arf locus is a barrier for iPS cell reprogramming. Nature. 2009;460(7259):1136-1139.
272. Marión RM, Strati K, Li H, Murga M, Blanco R, Ortega S, et al. A p53-mediated DNA damage response limits reprogramming to ensure iPS cell genomic integrity. Nature. 2009;460(7259):1149-1153.
273. Utikal J, Polo JM, Stadtfeld M, Maherali N, Kulalert W, Walsh RM, et al. Immortalization eliminates a roadblock during cellular reprogramming into iPS cells. Nature. 2009;460(7259):1145-1148.
274. Sarig R, Rivlin N, Brosh R, Bornstein C, Kamer I, Ezra O, et al. Mutant p53 facilitates somatic cell reprogramming and augments the malignant potential of reprogrammed cells. J Exp Med. 2010;207(10):2127-2140.
275. Stein Y, Aloni-Grinstein R, Rotter V. Mutant p53-a potential player in shaping the tumor-stroma crosstalk. J Mol Cell Biol. 2019;11(7):600-604.
276. Kieser A, Weich HA, Brandner G, Marmé D, Kolch W. Mutant p53 potentiates protein kinase C induction of vascular endothelial growth factor expression. Oncogene. 1994;9(3):963-969.
277. Fontemaggi G, Dell'Orso S, Trisciuoglio D, Shay T, Melucci E, Fazi F, et al. The execution of the transcriptional axis mutant p53, E2F1 and ID4 promotes tumor neo-angiogenesis. Nat Struct Mol Biol. 2009;16(10):1086-1093.
278. Pruszko M, Milano E, Forcato M, Donzelli S, Ganci F, Di Agostino S, et al. The mutant p53-ID4 complex controls VEGFA isoforms by recruiting lncRNA MALAT1. EMBO Rep. 2017;18(8):1331-1351.
279. Neilsen PM, Noll JE, Suetani RJ, Schulz RB, Al-Ejeh F, Evdokiou A, et al. Mutant p53 uses p63 as a molecular chaperone to alter gene expression and induce a pro-invasive secretome. Oncotarget. 2011;2(12):1203-1217.
280. Amelio I, Mancini M, Petrova V, Cairns RA, Vikhreva P, Nicolai S, et al. p53 mutants cooperate with HIF-1 in transcriptional regulation of extracellular matrix components to promote tumor progression. Proc Natl Acad Sci U S A. 2018;115(46):e10869-e10878.
281. Madar S, Harel E, Goldstein I, Stein Y, Kogan-Sakin I, Kamer I, et al. Mutant p53 attenuates the anti-tumorigenic activity of fibroblasts-secreted interferon beta. PLoS One. 2013;8(4):e61353.
282. Blagih J, Buck MD, Vousden KH. p53, cancer and the immune response. J Cell Sci. 2020;133(5):jcs237453.
283. Dong ZY, Zhong WZ, Zhang XC, Su J, Xie Z, Liu SY, et al. Potential Predictive Value of TP53 and KRAS Mutation Status for Response to PD-1 Blockade Immunotherapy in Lung Adenocarcinoma. Clin Cancer Res. 2017;23(12):3012-3024.
284. Cooks T, Pateras IS, Tarcic O, Solomon H, Schetter AJ, Wilder S, et al. Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. Cancer Cell. 2013;23(5):634-6346.
285. Di Minin G, Bellazzo A, Dal Ferro M, Chiaruttini G, Nuzzo S, Bicciato S, et al. Mutant p53 reprograms TNF signaling in cancer cells through interaction with the tumor suppressor DAB2IP. Mol Cell. 2014;56(5):617-629.
286. Ubertini V, Norelli G, D'Arcangelo D, Gurtner A, Cesareo E, Baldari S, et al. Mutant p53 gains new function in promoting inflammatory signals by repression of the secreted interleukin-1 receptor antagonist. Oncogene. 2015;34(19):2493-2504.
287. Cooks T, Pateras IS, Jenkins LM, Patel KM, Robles AI, Morris J, et al. Mutant p53 cancers reprogram macrophages to tumor supporting macrophages via exosomal miR-1246. Nat Commun. 2018;9(1):771.
288. He C, Li L, Guan X, Xiong L, Miao X. Mutant p53 Gain of Function and Chemoresistance: The Role of Mutant p53 in Response to Clinical Chemotherapy. Chemotherapy. 2017;62(1):43-53.
289. Zhou X, Hao Q, Lu H. Mutant p53 in cancer therapy-the barrier or the path. J Mol Cell Biol. 2019;11(4):293-305.
290. Chin KV, Ueda K, Pastan I, Gottesman MM. Modulation of activity of the promoter of the human MDR1 gene by Ras and p53. Science. 1992;255(5043):459-462.
291. Sampath J, Sun D, Kidd VJ, Grenet J, Gandhi A, Shapiro LH, et al. Mutant p53 cooperates with ETS and selectively up-regulates human MDR1 not MRP1. J Biol Chem. 2001;276(42):39359-39367.
292. Alam SK, Yadav VK, Bajaj S, Datta A, Dutta SK, Bhattacharyya M, et al. DNA damage-induced ephrin-B2 reverse signaling promotes chemoresistance and drives EMT in colorectal carcinoma harboring mutant p53. Cell Death Differ. 2016;23(4):707-722.
293. Xu J, Wang J, Hu Y, Qian J, Xu B, Chen H, et al. Unequal prognostic potentials of p53 gain-of-function mutations in human cancers associate with drug-metabolizing activity. Cell Death Dis. 2014;5(3):e1108.
294. Di Como CJ, Gaiddon C, Prives C. p73 function is inhibited by tumor-derived p53 mutants in mammalian cells. Mol Cell Biol. 1999;19(2):1438-1449.
295. Zhou G, Wang J, Zhao M, Xie TX, Tanaka N, Sano D, et al. Gain-of-function mutant p53 promotes cell growth and cancer cell metabolism via inhibition of AMPK activation. Mol Cell. 2014;54(6):960-974.
296. Cordani M, Oppici E, Dando I, Butturini E, Dalla Pozza E, Nadal-Serrano M, et al. Mutant p53 proteins counteract autophagic mechanism sensitizing cancer cells to mTOR inhibition. Mol Oncol. 2016;10(7):1008-1029.
297. Donzelli S, Fontemaggi G, Fazi F, Di Agostino S, Padula F, Biagioni F, et al. MicroRNA-128-2 targets the transcriptional repressor E2F5 enhancing mutant p53 gain of function. Cell Death Differ. 2012;19(6):1038-1048.
298. Masciarelli S, Fontemaggi G, Di Agostino S, Donzelli S, Carcarino E, Strano S, et al. Gain-of-function mutant p53 downregulates miR-223 contributing to chemoresistance of cultured tumor cells. Oncogene. 2014;33(12):1601-1608.
299. Cordani M, Butera G, Pacchiana R, Donadelli M. Molecular interplay between mutant p53 proteins and autophagy in cancer cells. Biochim Biophys Acta Rev Cancer. 2017;1867(1):19-28.
300. Shi Y, Norberg E, Vakifahmetoglu-Norberg H. Mutant p53 as a Regulator and Target of Autophagy. Front Oncol. 2020;10:607149.
301. Morselli E, Tasdemir E, Maiuri MC, Galluzzi L, Kepp O, Criollo A, et al. Mutant p53 protein localized in the cytoplasm inhibits autophagy. Cell Cycle. 2008;7(19):3056-3061.

302. Kiaris H, Chatzistamou I, Trimis G, Frangou-Plemmenou M, Pafiti-Kondi A, Kalofoutis A. Evidence for nonautonomous effect of p53 tumor suppressor in carcinogenesis. Cancer Res. 2005;65(5):1627-1630.
303. Lujambio A, Akkari L, Simon J, Grace D, Tschaharganeh DF, Bolden JE, et al. Non-cell-autonomous tumor suppression by p53. Cell. 2013;153(2):449-460.
304. Cui Y, Guo G. Immunomodulatory Function of the Tumor Suppressor p53 in Host Immune Response and the Tumor Microenvironment. Int J Mol Sci. 2016;17(11):1942.
305. Khalaf K, Hana D, Chou JT, Singh C, Mackiewicz A, Kaczmarek M. Aspects of the Tumor Microenvironment Involved in Immune Resistance and Drug Resistance. Front Immunol. 2021;12:656364.
306. Leung HW, Zhao SM, Yue GG, Lee JK, Fung KP, Leung PC, et al. RA-XII inhibits tumour growth and metastasis in breast tumour-bearing mice via reducing cell adhesion and invasion and promoting matrix degradation. Sci Rep. 2015;5: 16985.
307. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: Regulators of the tumor microenvironment. Cell. 2010;141(1):52-67.
308. Mentlein R, Hattermann K, Held-Feindt J. Lost in disruption: Role of proteases in glioma invasion and progression. Biochim Biophys Acta. 2012;1825(2):178-185.
309. Melendez-Zajgla J, Del Pozo L, Ceballos G, Maldonado V. Tissue inhibitor of metalloproteinases-4. The road less traveled. Mol Cancer. 2008;7:85.
310. Cordani M, Pacchiana R, Butera G, D'Orazi G, Scarpa A, Donadelli M. Mutant p53 proteins alter cancer cell secretome and tumour microenvironment: Involvement in cancer invasion and metastasis. Cancer Letters. 2016;376(2):303-309.
311. Novo D, Heath N, Mitchell L, Caligiuri G, MacFarlane A, Reijmer D, et al. Mutant p53s generate pro-invasive niches by influencing exosome podocalyxin levels. Nature Communications. 2018;9(1):5069.
312. Sun Y, Cheung JM, Martel-Pelletier J, Pelletier JP, Wenger L, Altman RD, et al. Wild Type and Mutant p53 Differentially Regulate the Gene Expression of Human Collagenase-3 (hMMP-13)*. Journal of Biological Chemistry. 2000;275(15):11327-11332.
313. Cohen M, Wuillemin C, Irion O, Bischof P. Regulation of MMP-9 by p53 in first trimester cytotrophoblastic cells. Hum Reprod. 2008;23(10):2273-2281.
314. Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011;144(5):646-674.
315. Daniel D, Meyer-Morse N, Bergsland EK, Dehne K, Coussens LM, Hanahan D. Immune enhancement of skin carcinogenesis by CD4+ T cells. J Exp Med. 2003;197(8):1017-1028.
316. Ardestani SK, Inserra P, Solkoff D, Watson RR. The role of cytokines and chemokines on tumor progression: A review. Cancer Detect Prev. 1999;233:215-225.
317. Wilson J, Balkwill F. The role of cytokines in the epithelial cancer microenvironment. Semin Cancer Biol. 2002;12(2):113-120.
318. Hanahan D, Weinberg RA. The Hallmarks of Cancer. Cell. 2000;100(1):57-70.
319. Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature. 2001;410(6824):50-56.
320. Scotton CJ, Wilson JL, Milliken D, Stamp G, Balkwill FR. Epithelial cancer cell migration: A role for chemokine receptors? Cancer Res. 2001;61(13):4961-4965.
321. Moskovits N, Kalinkovich A, Bar J, Lapidot T, Oren M. p53 Attenuates cancer cell migration and invasion through repression of SDF-1/CXCL12 expression in stromal fibroblasts. Cancer Res. 2006;66(22):10671-10676.
322. Mehta SA, Christopherson KW, Bhat-Nakshatri P, Goulet RJ Jr., Broxmeyer HE, Kopelovich L, et al. Negative regulation of chemokine receptor CXCR4 by tumor suppressor p53 in breast cancer cells: Implications of p53 mutation or isoform expression on breast cancer cell invasion. Oncogene. 2007;26(23):3329-3337.
323. Yeudall WA, Vaughan CA, Miyazaki H, Ramamoorthy M, Choi MY, Chapman CG, et al. Gain-of-function mutant p53 upregulates CXC chemokines and enhances cell migration. Carcinogenesis. 2012;33(2):442-451.
324. Ben-Neriah Y, Karin M. Inflammation meets cancer, with NF-κB as the matchmaker. Nat Immunol. 2011;12(8):715-723.
325. Karin M, Greten FR. NF-kappaB: Linking inflammation and immunity to cancer development and progression. Nat Rev Immunol. 2005;5(10):749-759.
326. Richmond A, Fan GH, Dhawan P, Yang J. How do chemokine/chemokine receptor activations affect tumorigenesis? Novartis Found Symp. 2004;256:74-89.
327. Cooks T, Pateras IS, Tarcic O, Solomon H, Schetter AJ, Wilder S, et al. Mutant p53 prolongs NF-κB activation and promotes chronic inflammation and inflammation-associated colorectal cancer. Cancer Cell. 2013;23(5):634-646.
328. Scian MJ, Stagliano KE, Ellis MA, Hassan S, Bowman M, Miles MF, et al. Modulation of gene expression by tumor-derived p53 mutants. Cancer Res. 2004;64(20):7447-7454.
329. Yan W, Chen X. Identification of GRO1 as a critical determinant for mutant p53 gain of function. J Biol Chem. 2009;284(18):12178-12187.
330. Apte RN, Voronov E. Is interleukin-1 a good or bad 'guy' in tumor immunobiology and immunotherapy? Immunol Rev. 2008;222:222-241.
331. Schreuder H, Tardif C, Trump-Kallmeyer S, Soffientini A, Sarubbi E, Akeson A, et al. A new cytokine-receptor binding mode revealed by the crystal structure of the IL-1 receptor with an antagonist. Nature. 1997;386(6621):194-200.
332. Ubertini V, Norelli G, D'Arcangelo D, Gurtner A, Cesareo E, Baldari S, et al. Mutant p53 gains new function in promoting inflammatory signals by repression of the secreted interleukin-1 receptor antagonist. Oncogene. 2015;34(19):2493-2504.
333. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309-314.
334. Stubbs M, McSheehy PM, Griffiths JR, Bashford CL. Causes and consequences of tumour acidity and implications for treatment. Mol Med Today. 2000;6(1):15-19.
335. Swietach P, Vaughan-Jones RD, Harris AL. Regulation of tumor pH and the role of carbonic anhydrase 9. Cancer and Metastasis Reviews. 2007;26(2):299-310.
336. Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 2006;126(1):107-120.
337. Zhang C, Lin M, Wu R, Wang X, Yang B, Levine AJ, et al. Parkin, a p53 target gene, mediates the role of p53 in glucose

metabolism and the Warburg effect. Proc Natl Acad Sci U S A. 2011;108(39):16259-16264.
338. Solomon H, Madar S, Rotter V. Mutant p53 gain of function is interwoven into the hallmarks of cancer. J Pathol. 2011;225(4):475-478.
339. Addadi Y, Moskovits N, Granot D, Lozano G, Carmi Y, Apte RN, et al. p53 status in stromal fibroblasts modulates tumor growth in an SDF1-dependent manner. Cancer Res. 2010;70(23):9650-9658.
340. Wang D, Wang H, Brown J, Daikoku T, Ning W, Shi Q, et al. CXCL1 induced by prostaglandin E2 promotes angiogenesis in colorectal cancer. J Exp Med. 2006;203(4):941-951.
341. Ferrara N, Kerbel RS. Angiogenesis as a therapeutic target. Nature. 2005;438(7070):967-974.
342. Folkman J. Angiogenesis: An organizing principle for drug discovery? Nat Rev Drug Discov. 2007;6(4):273-286.
343. Lyden D, Young AZ, Zagzag D, Yan W, Gerald W, O'Reilly R, et al. Id1 and Id3 are required for neurogenesis, angiogenesis and vascularization of tumour xenografts. Nature. 1999;401(6754):670-677.
344. Caunt M, Hu L, Tang T, Brooks PC, Ibrahim S, Karpatkin S. Growth-regulated oncogene is pivotal in thrombin-induced angiogenesis. Cancer Res. 2006;66(8):4125-4132.
345. Waugh DJ, Wilson C. The interleukin-8 pathway in cancer. Clin Cancer Res. 2008;14(21):6735-6741.
346. Linderholm BK, Lindahl T, Holmberg L, Klaar S, Lennerstrand J, Henriksson R, et al. The expression of vascular endothelial growth factor correlates with mutant p53 and poor prognosis in human breast cancer. Cancer Res. 2001;61(5):2256-2260.
347. Narendran A, Ganjavi H, Morson N, Connor A, Barlow JW, Keystone E, et al. Mutant p53 in bone marrow stromal cells increases VEGF expression and supports leukemia cell growth. Exp Hematol. 2003;31(8):693-701.
348. Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. J Clin Oncol. 2003;21(2):383-391.
349. Downing S, Bumak C, Nixdorf S, Ow K, Russell P, Jackson P. Elevated levels of prostate-specific antigen (PSA) in prostate cancer cells expressing mutant p53 is associated with tumor metastasis. Mol Carcinog. 2003;38(3):130-140.
350. Gurova KV, Roklin OW, Krivokrysenko VI, Chumakov PM, Cohen MB, Feinstein E, et al. Expression of prostate specific antigen (PSA) is negatively regulated by p53. Oncogene. 2002;21(1):153-157.
351. Chenau J, Michelland S, de Fraipont F, Josserand V, Coll JL, Favrot MC, et al. The cell line secretome, a suitable tool for investigating proteins released in vivo by tumors: Application to the study of p53-modulated proteins secreted in lung cancer cells. J Proteome Res. 2009;8(10):4579-4591.
352. Nejman D, Livyatan I, Fuks G, Gavert N, Zwang Y, Geller LT, et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science. 2020;368(6494):973-980.
353. Fu A, Yao B, Dong T, Chen Y, Yao J, Liu Y, et al. Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer. Cell. 2022;185(8):1356-1372. e26.
354. Narunsky-Haziza L, Sepich-Poore GD, Livyatan I, Asraf O, Martino C, Nejman D, et al. Pan-cancer analyses reveal cancer-type-specific fungal ecologies and bacteriome interactions. Cell. 2022;185(20):3789-3806. e17.
355. Liu NN, Yi CX, Wei LQ, Zhou JA, Jiang T, Hu CC, et al. The intratumor mycobiome promotes lung cancer progression via myeloid-derived suppressor cells. Cancer Cell. 2023;41(11):1927-1944. e9.
356. Dohlman AB, Klug J, Mesko M, Gao IH, Lipkin SM, Shen X, et al. A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors. Cell. 2022;185(20):3807-3822. e12.
357. Greathouse KL, White JR, Vargas AJ, Bliskovsky VV, Beck JA, von Muhlinen N, et al. Interaction between the microbiome and TP53 in human lung cancer. Genome Biol. 2018;19(1):123.
358. Dong H, Tan Q, Xu Y, Zhu Y, Yao Y, Wang Y, et al. Convergent alteration of lung tissue microbiota and tumor cells in lung cancer. iScience. 2022;25(1):103638.
359. Aschtgen MS, Fragkoulis K, Sanz G, Normark S, Selivanova G, Henriques-Normark B, et al. Enterobacteria impair host p53 tumor suppressor activity through mRNA destabilization. Oncogene. 2022;41(15):2173-2186.
360. Kadosh E, Snir-Alkalay I, Venkatachalam A, May S, Lasry A, Elyada E, et al. The gut microbiome switches mutant p53 from tumour-suppressive to oncogenic. Nature. 2020;586(7827):133-138.
361. Celardo I, Melino G, Amelio I. Commensal microbes and p53 in cancer progression. Biol Direct. 2020;15(1):25.
362. Li X, Heyer WD. Homologous recombination in DNA repair and DNA damage tolerance. Cell Res. 2008;18(1):99-113.
363. Costa L, Corre S, Michel V, Le Luel K, Fernandes J, Ziveri J, et al. USF1 defect drives p53 degradation during Helicobacter pylori infection and accelerates gastric carcinogenesis. Gut. 2020;69(9):1582-1591.
364. Buti L, Spooner E, Van der Veen AG, Rappuoli R, Covacci A, Ploegh HL. Helicobacter pylori cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. Proc Natl Acad Sci U S A. 2011;108(22):9238-9243.
365. LaRock DL, Chaudhary A, Miller SI. Salmonellae interactions with host processes. Nature Reviews Microbiology. 2015;13(4):191-205.
366. Wu S, Ye Z, Liu X, Zhao Y, Xia Y, Steiner A, et al. Salmonella typhimurium infection increases p53 acetylation in intestinal epithelial cells. Am J Physiol Gastrointest Liver Physiol. 2010;298(5):G784-G794.
367. Zhao LY, Mei JX, Yu G, Lei L, Zhang WH, Liu K, et al. Role of the gut microbiota in anticancer therapy: From molecular mechanisms to clinical applications. Signal Transduct Target Ther. 2023;8(1):201.
368. Wolff S, Erster S, Palacios G, Moll UM. p53's mitochondrial translocation and MOMP action is independent of Puma and Bax and severely disrupts mitochondrial membrane integrity. Cell Res. 2008;18(7):733-744.
369. Leu JI, Dumont P, Hafey M, Murphy ME, George DL. Mitochondrial p53 activates Bak and causes disruption of a Bak-Mcl1 complex. Nat Cell Biol. 2004;6(5):443-450.
370. McDermott U, Longley DB, Galligan L, Allen W, Wilson T, Johnston PG. Effect of p53 status and STAT1 on chemotherapy-induced, Fas-mediated apoptosis in colorectal cancer. Cancer Res. 2005;65(19):8951-8960.
371. Wong RP, Tsang WP, Chau PY, Co NN, Tsang TY, Kwok TT. p53-R273H gains new function in induction of drug resistance

through down-regulation of procaspase-3. Mol Cancer Ther. 2007;6(3):1054-1061.
372. Huang Y, Liu N, Liu J, Liu Y, Zhang C, Long S, et al. Mutant p53 drives cancer chemotherapy resistance due to loss of function on activating transcription of PUMA. Cell Cycle. 2019;18(24):3442-3455.
373. Irwin MS, Kondo K, Marin MC, Cheng LS, Hahn WC, Kaelin WG. Chemosensitivity linked to p73 function. Cancer Cell. 2003;3(4):403-410.
374. Cho Y-H, Ro EJ, Yoon J-S, Mizutani T, Kang D-W, Park J-C, et al. 5-FU promotes stemness of colorectal cancer via p53-mediated WNT/β-catenin pathway activation. Nature Communications. 2020;11(1):5321.
375. Yang Y, Yuan H, Zhao L, Guo S, Hu S, Tian M, et al. Targeting the miR-34a/LRPPRC/MDR1 axis collapse the chemoresistance in P53 inactive colorectal cancer. Cell Death Differ. 2022;29(11):2177-2189.
376. Pawlik TM, Keyomarsi K. Role of cell cycle in mediating sensitivity to radiotherapy. Int J Radiat Oncol Biol Phys. 2004;59(4):928-942.
377. Fei P, El-Deiry WS. P53 and radiation responses. Oncogene. 2003;22(37):5774-5783.
378. Pearson S, Jia H, Kandachi K. China approves first gene therapy. Nat Biotechnol. 2004;22(1):3-4.
379. Gudkov AV, Komarova EA. The role of p53 in determining sensitivity to radiotherapy. Nature Reviews Cancer. 2003;3(2):117-129.
380. Huang RX, Zhou PK. DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. Signal Transduct Target Ther. 2020;5(1):60.
381. Lv L, Zhou M, Zhang J, Liu F, Qi L, Zhang S, et al. SOX6 suppresses the development of lung adenocarcinoma by regulating expression of p53, p21CIPI, cyclin D1 and β-catenin. FEBS Open Bio. 2020;10(1):135-146.
382. Tanoue Y, Toyoda T, Sun J, Mustofa MK, Tateishi C, Endo S, et al. Differential Roles of Rad18 and Chk2 in Genome Maintenance and Skin Carcinogenesis Following UV Exposure. J Invest Dermatol. 2018;138(12):2550-2557.
383. Luo L, Gao W, Wang J, Wang D, Peng X, Jia Z, et al. Study on the Mechanism of Cell Cycle Checkpoint Kinase 2 (CHEK2) Gene Dysfunction in Chemotherapeutic Drug Resistance of Triple Negative Breast Cancer Cells. Med Sci Monit. 2018;24:3176-3183.
384. Xu L, Pirollo KF, Chang EH. Tumor-targeted p53-gene therapy enhances the efficacy of conventional chemo/radiotherapy. J Control Release. 2001;74(1-3):115-128.
385. Reinhardt HC, Aslanian AS, Lees JA, Yaffe MB. p53-deficient cells rely on ATM- and ATR-mediated checkpoint signaling through the p38MAPK/MK2 pathway for survival after DNA damage. Cancer Cell. 2007;11(2):175-189.
386. Morandell S, Reinhardt HC, Cannell IG, Kim JS, Ruf DM, Mitra T, et al. A reversible gene-targeting strategy identifies synthetic lethal interactions between MK2 and p53 in the DNA damage response in vivo. Cell Rep. 2013;5(4):868-877.
387. Reinhardt HC, Jiang H, Hemann MT, Yaffe MB. Exploiting synthetic lethal interactions for targeted cancer therapy. Cell Cycle. 2009;8(19):3112-3119.
388. Andrysik Z, Kim J, Tan AC, Espinosa JM. A genetic screen identifies TCF3/E2A and TRIAP1 as pathway-specific regulators of the cellular response to p53 activation. Cell Rep. 2013;3(5):1346-1354.
389. Kottemann MC, Bale AE. Characterization of DNA damage-dependent cell cycle checkpoints in a menin-deficient model. DNA Repair (Amst). 2009;8(8):944-952.
390. Barnum KJ, O'Connell MJ. Cell cycle regulation by checkpoints. Methods Mol Biol. 2014;1170:29-40.
391. Nagasawa H, Keng P, Maki C, Yu Y, Little JB. Absence of a radiation-induced first-cycle G1-S arrest in p53+ human tumor cells synchronized by mitotic selection. Cancer Res. 1998;58(9):2036-2041.
392. Fabbro M, Savage K, Hobson K, Deans AJ, Powell SN, McArthur GA, et al. BRCA1-BARD1 complexes are required for p53Ser-15 phosphorylation and a G1/S arrest following ionizing radiation-induced DNA damage. J Biol Chem. 2004;279(30):31251-31258.
393. Yoon HS, Chen X, Yang VW. Kruppel-like factor 4 mediates p53-dependent G1/S cell cycle arrest in response to DNA damage. J Biol Chem. 2003;278(4):2101-2105.
394. Cui D, Xiong X, Shu J, Dai X, Sun Y, Zhao Y. FBXW7 Confers Radiation Survival by Targeting p53 for Degradation. Cell Rep. 2020;30(2):497-509. e4.
395. Falck J, Petrini JH, Williams BR, Lukas J, Bartek J. The DNA damage-dependent intra-S phase checkpoint is regulated by parallel pathways. Nat Genet. 2002;30(3):290-294.
396. Wang B. Analyzing cell cycle checkpoints in response to ionizing radiation in mammalian cells. Methods Mol Biol. 2014;1170:313-320.
397. Kennedy MC, Lowe SW. Mutant p53: It's not all one and the same. Cell Death and Differentiation. 2022;29:983-987.
398. Kong X, Yu D, Wang Z, Li S. Relationship between p53 status and the bioeffect of ionizing radiation. Oncol Lett. 2021;22(3):661.
399. Huang R, Zhou PK. DNA damage repair: Historical perspectives, mechanistic pathways and clinical translation for targeted cancer therapy. Signal Transduct Target Ther. 2021;6(1):254.
400. Carlsen L, El-Deiry WS. Differential p53-Mediated Cellular Responses to DNA-Damaging Therapeutic Agents. Int J Mol Sci. 2021;22(21):11828.
401. Beckta JM, Ahmad SF, Yang H, Valerie K. Revisiting p53 for cancer-specific chemo- and radiotherapy: Ten years after. Cell Cycle. 2014;13(5):710-713.
402. Werbrouck C, Evangelista CCS, Lobón-Iglesias MJ, Barret E, Le Teuff G, Merlevede J, et al. TP53 Pathway Alterations Drive Radioresistance in Diffuse Intrinsic Pontine Gliomas (DIPG). Clin Cancer Res. 2019;25(22):6788-800.
403. O'Connor PM, Jackman J, Bae I, Myers TG, Fan S, Mutoh M, et al. Characterization of the p53 tumor suppressor pathway in cell lines of the National Cancer Institute anticancer drug screen and correlations with the growth-inhibitory potency of 123 anticancer agents. Cancer Res. 1997;57(19):4285-4300.
404. Hinata N, Shirakawa T, Zhang Z, Matsumoto A, Fujisawa M, Okada H, et al. Radiation induces p53-dependent cell apoptosis in bladder cancer cells with wild-type- p53 but not in p53-mutated bladder cancer cells. Urol Res. 2003;31(6):387-396.
405. Kuerbitz SJ, Plunkett BS, Walsh WV, Kastan MB. Wild-type p53 is a cell cycle checkpoint determinant following irradiation. Proc Natl Acad Sci U S A. 1992;89(16):7491-7495.

406. Quick QA, Gewirtz DA. An accelerated senescence response to radiation in wild-type p53 glioblastoma multiforme cells. J Neurosurg. 2006;105(1):111-118.
407. Concin N, Zeillinger C, Stimpfel M, Schiebel I, Tong D, Wolff U, et al. p53-dependent radioresistance in ovarian carcinoma cell lines. Cancer Lett. 2000;150(2):191-199.
408. Dey S, Spring PM, Arnold S, Valentino J, Chendil D, Regine WF, et al. Low-dose fractionated radiation potentiates the effects of Paclitaxel in wild-type and mutant p53 head and neck tumor cell lines. Clin Cancer Res. 2003;9(4):1557-1565.
409. Zheng X, Liu B, Liu X, Li P, Zhang P, Ye F, et al. PERK Regulates the Sensitivity of Hepatocellular Carcinoma Cells to High-LET Carbon Ions via either Apoptosis or Ferroptosis. J Cancer. 2022;13(2):669-680.
410. Ishikawa H, Mitsuhashi N, Sakurai H, Maebayashi K, Niibe H. The effects of p53 status and human papillomavirus infection on the clinical outcome of patients with stage IIIB cervical carcinoma treated with radiation therapy alone. Cancer. 2001;91(1):80-89.
411. Miyasaka A, Oda K, Ikeda Y, Sone K, Fukuda T, Inaba K, et al. PI3K/mTOR pathway inhibition overcomes radioresistance via suppression of the HIF1-α/VEGF pathway in endometrial cancer. Gynecol Oncol. 2015;138(1):174-180.
412. Lee JM, Bernstein A. p53 mutations increase resistance to ionizing radiation. Proc Natl Acad Sci U S A. 1993;90(12):5742-5746.
413. Kawashima K, Mihara K, Usuki H, Shimizu N, Namba M. Transfected mutant p53 gene increases X-ray-induced cell killing and mutation in human fibroblasts immortalized with 4-nitroquinoline 1-oxide but does not induce neoplastic transformation of the cells. Int J Cancer. 1995;61(1):76-79.
414. Biard DS, Martin M, Rhun YL, Duthu A, Lefaix JL, May E, et al. Concomitant p53 gene mutation and increased radiosensitivity in rat lung embryo epithelial cells during neoplastic development. Cancer Res. 1994;54(13):3361-3364.
415. Okaichi K, Ide-Kanematsu M, Izumi N, Morita N, Okumura Y, Ihara M. Variations in sensitivity to ionizing radiation in relation to p53 mutation point. Anticancer Res. 2008;28(5a):2687-2690.
416. Okaichi K, Nose K, Kotake T, Izumi N, Kudo T. Phosphorylation of p53 modifies sensitivity to ionizing radiation. Anticancer Res. 2011;31(6):2255-2258.
417. Tada M, Matsumoto R, Iggo RD, Onimaru R, Shirato H, Sawamura Y, et al. Selective sensitivity to radiation of cerebral glioblastomas harboring p53 mutations. Cancer Res. 1998;58(9):1793-1797.
418. Cheng G, Kong D, Hou X, Liang B, He M, Liang N, et al. The tumor suppressor, p53, contributes to radiosensitivity of lung cancer cells by regulating autophagy and apoptosis. Cancer Biother Radiopharm. 2013;28(2):153-159.
419. Walerych D, Lisek K, Sommaggio R, Piazza S, Ciani Y, Dalla E, et al. Proteasome machinery is instrumental in a common gain-of-function program of the p53 missense mutants in cancer. Nat Cell Biol. 2016;18(8):897-909.
420. Lauwen MM, Zwaveling S, de Quartel L, Ferreira Mota SC, Grashorn JA, Melief CJ, et al. Self-tolerance does not restrict the CD4+ T-helper response against the p53 tumor antigen. Cancer Res. 2008;68(3):893-900.
421. Xue Y, Barker N, Hoon S, He P, Thakur T, Abdeen SR, et al. Bortezomib Stabilizes and Activates p53 in Proliferative Compartments of Both Normal and Tumor Tissues In Vivo. Cancer Res. 2019;79(14):3595-3607.
422. Chikamatsu K, Nakano K, Storkus WJ, Appella E, Lotze MT, Whiteside TL, et al. Generation of anti-p53 cytotoxic T lymphocytes from human peripheral blood using autologous dendritic cells. Clin Cancer Res. 1999;5(6):1281-1288.
423. Röpke M, Hald J, Guldberg P, Zeuthen J, Nørgaard L, Fugger L, et al. Spontaneous human squamous cell carcinomas are killed by a human cytotoxic T lymphocyte clone recognizing a wild-type p53-derived peptide. Proc Natl Acad Sci U S A. 1996;93(25):14704-14707.
424. Vierboom MP, Nijman HW, Offringa R, van der Voort EI, van Hall T, van den Broek L, et al. Tumor eradication by wild-type p53-specific cytotoxic T lymphocytes. J Exp Med. 1997;186(5):695-704.
425. Speetjens FM, Kuppen PJ, Welters MJ, Essahsah F, Voet van den Brink AM, Lantrua MG, et al. Induction of p53-specific immunity by a p53 synthetic long peptide vaccine in patients treated for metastatic colorectal cancer. Clin Cancer Res. 2009;15(3):1086-1095.
426. Vermeij R, Leffers N, Hoogeboom BN, Hamming IL, Wolf R, Reyners AK, et al. Potentiation of a p53-SLP vaccine by cyclophosphamide in ovarian cancer: A single-arm phase II study. Int J Cancer. 2012;131(5):e670-e680.
427. Hardwick NR, Carroll M, Kaltcheva T, Qian D, Lim D, Leong L, et al. p53MVA therapy in patients with refractory gastrointestinal malignancies elevates p53-specific CD8+ T-cell responses. Clin Cancer Res. 2014;20(17):4459-4470.
428. Hardwick NR, Frankel P, Ruel C, Kilpatrick J, Tsai W, Kos F, et al. p53-Reactive T Cells Are Associated with Clinical Benefit in Patients with Platinum-Resistant Epithelial Ovarian Cancer After Treatment with a p53 Vaccine and Gemcitabine Chemotherapy. Clin Cancer Res. 2018;24(6):1315-1325.
429. Barfoed AM, Petersen TR, Kirkin AF, Thor Straten P, Claesson MH, Zeuthen J. Cytotoxic T-lymphocyte clones, established by stimulation with the HLA-A2 binding p5365-73 wild type peptide loaded on dendritic cells In vitro, specifically recognize and lyse HLA-A2 tumour cells overexpressing the p53 protein. Scand J Immunol. 2000;51(2):128-133.
430. Antonia SJ, Mirza N, Fricke I, Chiappori A, Thompson P, Williams N, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. Clin Cancer Res. 2006;12(3 Pt 1):878-887.
431. Chiappori AA, Soliman H, Janssen WE, Antonia SJ, Gabrilovich DI. INGN-225: A dendritic cell-based p53 vaccine (Ad.p53-DC) in small cell lung cancer: Observed association between immune response and enhanced chemotherapy effect. Expert Opin Biol Ther. 2010;10(6):983-991.
432. Chiappori AA, Williams CC, Gray JE, Tanvetyanon T, Haura EB, Creelan BC, et al. Randomized-controlled phase II trial of salvage chemotherapy after immunization with a TP53-transfected dendritic cell-based vaccine (Ad.p53-DC) in patients with recurrent small cell lung cancer. Cancer Immunol Immunother. 2019;68(3):517-527.
433. Met O, Balslev E, Flyger H, Svane IM. High immunogenic potential of p53 mRNA-transfected dendritic cells in patients with primary breast cancer. Breast Cancer Res Treat. 2011;125(2):395-406.

434. Rosenberg SA, Yang JC, Sherry RM, Kammula US, Hughes MS, Phan GQ, et al. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res. 2011;17(13):4550-4557.
435. Rosenberg SA, Restifo NP, Yang JC, Morgan RA, Dudley ME. Adoptive cell transfer: A clinical path to effective cancer immunotherapy. Nat Rev Cancer. 2008;8(4):299-308.
436. Theoret MR, Cohen CJ, Nahvi AV, Ngo LT, Suri KB, Powell DJ, et al. Relationship of p53 overexpression on cancers and recognition by anti-p53 T cell receptor-transduced T cells. Hum Gene Ther. 2008;19(11):1219-1232.
437. Yanuck M, Carbone DP, Pendleton CD, Tsukui T, Winter SF, Minna JD, et al. A mutant p53 tumor suppressor protein is a target for peptide-induced CD8+ cytotoxic T-cells. Cancer Res. 1993;53(14):3257-3261.
438. Yu Z, Liu X, McCarty TM, Diamond DJ, Ellenhorn JD. The use of transgenic mice to generate high affinity p53 specific cytolytic T cells. J Surg Res. 1997;69(2):337-343.
439. Malekzadeh P, Pasetto A, Robbins PF, Parkhurst MR, Paria BC, Jia L, et al. Neoantigen screening identifies broad TP53 mutant immunogenicity in patients with epithelial cancers. J Clin Invest. 2019;129(3):1109-1114.
440. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science. 2011;331(6024):1612-1616.
441. Li D, Bentley C, Anderson A, Wiblin S, Cleary KLS, Koustoulidou S, et al. Development of a T-cell Receptor Mimic Antibody against Wild-Type p53 for Cancer Immunotherapy. Cancer Res. 2017;77(10):2699-2711.
442. Low L, Goh A, Koh J, Lim S, Wang CI. Targeting mutant p53-expressing tumours with a T cell receptor-like antibody specific for a wild-type antigen. Nat Commun. 2019;10(1):5382.
443. Cheever MA, Allison JP, Ferris AS, Finn OJ, Hastings BM, Hecht TT, et al. The prioritization of cancer antigens: A national cancer institute pilot project for the acceleration of translational research. Clin Cancer Res. 2009;15(17):5323-5337.
444. Balachandran VP, Łuksza M, Zhao JN, Makarov V, Moral JA, Remark R, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. Nature. 2017;551(7681):512-516.
445. Deniger DC, Pasetto A, Robbins PF, Gartner JJ, Prickett TD, Paria BC, et al. T-cell Responses to TP53 "Hotspot" Mutations and Unique Neoantigens Expressed by Human Ovarian Cancers. Clin Cancer Res. 2018;24(22):5562-5573.
446. Malekzadeh P, Yossef R, Cafri G, Paria BC, Lowery FJ, Jafferji M, et al. Antigen Experienced T Cells from Peripheral Blood Recognize p53 Neoantigens. Clin Cancer Res. 2020;26(6):1267-1276.
447. You G, Won J, Lee Y, Moon D, Park Y, Lee SH, et al. Bispecific Antibodies: A Smart Arsenal for Cancer Immunotherapies. Vaccines (Basel). 2021;9(7):724.
448. Hsiue EH, Wright KM, Douglass J, Hwang MS, Mog BJ, Pearlman AH, et al. Targeting a neoantigen derived from a common TP53 mutation. Science. 2021;371(6533):eabc8697.
449. Cortez MA, Ivan C, Valdecanas D, Wang X, Peltier HJ, Ye Y, et al. PDL1 Regulation by p53 via miR-34. J Natl Cancer Inst. 2016;108(1):djv303.
450. Textor S, Fiegler N, Arnold A, Porgador A, Hofmann TG, Cerwenka A. Human NK cells are alerted to induction of p53 in cancer cells by upregulation of the NKG2D ligands ULBP1 and ULBP2. Cancer Res. 2011;71(18):5998-6009.
451. Wellenstein MD, Coffelt SB, Duits DEM, van Miltenburg MH, Slagter M, de Rink I, et al. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature. 2019;572(7770):538-542.
452. Zhou X, Singh M, Sanz Santos G, Guerlavais V, Carvajal LA, Aivado M, et al. Pharmacologic Activation of p53 Triggers Viral Mimicry Response Thereby Abolishing Tumor Immune Evasion and Promoting Antitumor Immunity. Cancer Discov. 2021;11(12):3090-3105.
453. Maddalena M, Mallel G, Nataraj NB, Shreberk-Shaked M, Hassin O, Mukherjee S, et al. TP53 missense mutations in PDAC are associated with enhanced fibrosis and an immunosuppressive microenvironment. Proc Natl Acad Sci U S A. 2021;118(23):e2025631118.
454. Fang DD, Tang Q, Kong Y, Wang Q, Gu J, Fang X, et al. MDM2 inhibitor APG-115 synergizes with PD-1 blockade through enhancing antitumor immunity in the tumor microenvironment. J Immunother Cancer. 2019;7(1):327.
455. Tolcher AW, Reeves JA, McKean M, Chmielowski B, Beck JT, Shaheen MF, et al. Preliminary results of a phase II study of alrizomadlin (APG-115):a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients (pts) with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic (I-O) drugs. Journal of Clinical Oncology. 2021;39:2506.
456. Kim SS, Harford JB, Moghe M, Rait A, Chang EH. Combination with SGT-53 overcomes tumor resistance to a checkpoint inhibitor. Oncoimmunology. 2018;7(10):e1484982.
457. Chada S, Wiederhold D, Menander KB, Sellman B, Talbott M, Nemunaitis JJ, et al. Tumor suppressor immune gene therapy to reverse immunotherapy resistance. Cancer Gene Ther. 2022;29(6):825-834.
458. Jones SN, Roe AE, Donehower LA, Bradley A. Rescue of embryonic lethality in Mdm2-deficient mice by absence of p53. Nature. 1995;378(6553):206-208.
459. Montes de Oca Luna R, Wagner DS, Lozano G. Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p53. Nature. 1995;378(6553):203-206.
460. Parant J, Chavez-Reyes A, Little NA, Yan W, Reinke V, Jochemsen AG, et al. Rescue of embryonic lethality in Mdm4-null mice by loss of Trp53 suggests a nonoverlapping pathway with MDM2 to regulate p53. Nature Genetics. 2001;29(1):92-95.
461. Wade M, Li YC, Wahl GM. MDM2, MDMX and p53 in oncogenesis and cancer therapy. Nat Rev Cancer. 2013;13(2):83-96.
462. Momand J, Jung D, Wilczynski S, Niland J. The MDM2 gene amplification database. Nucleic Acids Res. 1998;26(15):3453-3459.
463. Vassilev LT, Vu BT, Graves B, Carvajal D, Podlaski F, Filipovic Z, et al. In vivo activation of the p53 pathway by small-molecule antagonists of MDM2. Science. 2004;303(5659):844-848.
464. Xiao ZX, Chen J, Levine AJ, Modjtahedi N, Xing J, Sellers WR, et al. Interaction between the retinoblastoma protein and the oncoprotein MDM2. Nature. 1995;375(6533):694-698.

465. Lau LM, Nugent JK, Zhao X, Irwin MS. HDM2 antagonist Nutlin-3 disrupts p73-HDM2 binding and enhances p73 function. Oncogene. 2008;27(7):997-1003.
466. Zhang Z, Wang H, Li M, Rayburn ER, Agrawal S, Zhang R. Stabilization of E2F1 protein by MDM2 through the E2F1 ubiquitination pathway. Oncogene. 2005;24(48):7238-7247.
467. Vu B, Wovkulich P, Pizzolato G, Lovey A, Ding Q, Jiang N, et al. Discovery of RG7112: A Small-Molecule MDM2 Inhibitor in Clinical Development. ACS Med Chem Lett. 2013;4(5):466-469.
468. Zhang Z, Ding Q, Liu JJ, Zhang J, Jiang N, Chu XJ, et al. Discovery of potent and selective spiroindolinone MDM2 inhibitor, RO8994, for cancer therapy. Bioorg Med Chem. 2014;22(15):4001-4009.
469. Ding Q, Zhang Z, Liu JJ, Jiang N, Zhang J, Ross TM, et al. Discovery of RG7388, a potent and selective p53-MDM2 inhibitor in clinical development. J Med Chem. 2013;56(14):5979-5983.
470. Montesinos P, Esteve J, Konopleva MY, Martinelli G, Ottmann OG, Rodríguez-Veiga R, et al. MIRROS: An ongoing randomized phase 3 trial of idasanutlin + ARA-C in patients with relapsed or refractory acute myeloid leukemia. Journal of Clinical Oncology. 2019;37((15),_suppl):TPS7063–TPS7063.
471. Tisato V, Voltan R, Gonelli A, Secchiero P, Zauli G. MDM2/X inhibitors under clinical evaluation: Perspectives for the management of hematological malignancies and pediatric cancer. J Hematol Oncol. 2017;10(1):133.
472. Ali AM, Atmaj J, Van Oosterwijk N, Groves MR, Dömling A. Stapled Peptides Inhibitors: A New Window for Target Drug Discovery. Comput Struct Biotechnol J. 2019;17:263-281.
473. Bernal F, Wade M, Godes M, Davis TN, Whitehead DG, Kung AL, et al. A stapled p53 helix overcomes HDMX-mediated suppression of p53. Cancer Cell. 2010;18(5):411-422.
474. Wachter F, Morgan AM, Godes M, Mourtada R, Bird GH, Walensky LD. Mechanistic validation of a clinical lead stapled peptide that reactivates p53 by dual HDM2 and HDMX targeting. Oncogene. 2017;36(15):2184-2190.
475. Chang YS, Graves B, Guerlavais V, Tovar C, Packman K, To KH, et al. Stapled α-helical peptide drug development: A potent dual inhibitor of MDM2 and MDMX for p53-dependent cancer therapy. Proc Natl Acad Sci U S A. 2013;110(36):E3445-E3454.
476. Carvajal LA, Neriah DB, Senecal A, Benard L, Thiruthuvanathan V, Yatsenko T, et al. Dual inhibition of MDMX and MDM2 as a therapeutic strategy in leukemia. Sci Transl Med. 2018;10(436):eaao3003.
477. Andrysik Z, Sullivan KD, Kieft JS, Espinosa JM. PPM1D suppresses p53-dependent transactivation and cell death by inhibiting the Integrated Stress Response. Nature communications. 2022;13(1):7400.
478. Li Q, Zhang Y, El-Naggar AK, Xiong S, Yang P, Jackson JG, et al. Therapeutic efficacy of p53 restoration in Mdm2-overexpressing tumors. Mol Cancer Res. 2014;12(6):901-911.
479. Ventura A, Kirsch DG, McLaughlin ME, Tuveson DA, Grimm J, Lintault L, et al. Restoration of p53 function leads to tumour regression in vivo. Nature. 2007;445(7128):661-665.
480. Martins CP, Brown-Swigart L, Evan GI. Modeling the therapeutic efficacy of p53 restoration in tumors. Cell. 2006;127(7):1323-1334.
481. Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, et al. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature. 2007;445(7128):656-660.
482. Ray-Coquard I, Blay JY, Italiano A, Le Cesne A, Penel N, Zhi J, et al. Effect of the MDM2 antagonist RG7112 on the P53 pathway in patients with MDM2-amplified, well-differentiated or dedifferentiated liposarcoma: An exploratory proof-of-mechanism study. Lancet Oncol. 2012;13(11):1133-1140.
483. Andreeff M, Kelly KR, Yee K, Assouline S, Strair R, Popplewell L, et al. Results of the Phase I Trial of RG7112, a Small-Molecule MDM2 Antagonist in Leukemia. Clin Cancer Res. 2016;22(4):868-876.
484. Hong B, van den Heuvel AP, Prabhu VV, Zhang S, El-Deiry WS. Targeting tumor suppressor p53 for cancer therapy: Strategies, challenges and opportunities. Curr Drug Targets. 2014;15(1):80-89.
485. Zawacka-Pankau J, Selivanova G. Pharmacological reactivation of p53 as a strategy to treat cancer. J Intern Med. 2015;277(2):248-259.
486. Parrales A, Iwakuma T. Targeting Oncogenic Mutant p53 for Cancer Therapy. Front Oncol. 2015;5:288.
487. Li Y, Wang Z, Chen Y, Petersen RB, Zheng L, Huang K. Salvation of the fallen angel: Reactivating mutant p53. Br J Pharmacol. 2019;176(7):817-831.
488. Silva JL, Lima CGS, Rangel LP, Ferretti GDS, Pauli FP, Ribeiro RCB, et al. Recent Synthetic Approaches towards Small Molecule Reactivators of p53. Biomolecules. 2020;10(4):635.
489. Loh SN. Follow the Mutations: Toward Class-Specific, Small-Molecule Reactivation of p53. Biomolecules. 2020;10(2):303.
490. Fra A, Yoboue ED, Sitia R. Cysteines as Redox Molecular Switches and Targets of Disease. Front Mol Neurosci. 2017;10:167.
491. Hallenbeck KK, Turner DM, Renslo AR, Arkin MR. Targeting Non-Catalytic Cysteine Residues Through Structure-Guided Drug Discovery. Curr Top Med Chem. 2017;17(1):4-15.
492. Zache N, Lambert JM, Rökaeus N, Shen J, Hainaut P, Bergman J, et al. Mutant p53 targeting by the low molecular weight compound STIMA-1. Mol Oncol. 2008;2(1):70-80.
493. Bykov VJ, Lambert JM, Hainaut P, Wiman KG. Mutant p53 rescue and modulation of p53 redox state. Cell Cycle. 2009;8(16):2509-2517.
494. Wassman CD, Baronio R, Demir Ö, Wallentine BD, Chen CK, Hall LV, et al. Computational identification of a transiently open L1/S3 pocket for reactivation of mutant p53. Nat Commun. 2013;4:1407.
495. Bykov VJ, Issaeva N, Shilov A, Hultcrantz M, Pugacheva E, Chumakov P, et al. Restoration of the tumor suppressor function to mutant p53 by a low-molecular-weight compound. Nat Med. 2002;8(3):282-288.
496. Bykov VJ, Issaeva N, Zache N, Shilov A, Hultcrantz M, Bergman J, et al. Reactivation of mutant p53 and induction of apoptosis in human tumor cells by maleimide analogs. J Biol Chem. 2005;280(34):30384-30391.
497. Bou-Hanna C, Jarry A, Lode L, Schmitz I, Schulze-Osthoff K, Kury S, et al. Acute cytotoxicity of MIRA-1/NSC19630, a mutant p53-reactivating small molecule, against human normal and cancer cells via a caspase-9-dependent apoptosis. Cancer Lett. 2015;359(2):211-217.
498. Joerger AC, Fersht AR. Structural biology of the tumor suppressor p53. Annu Rev Biochem. 2008;77:557-582.

499. Butler JS, Loh SN. Folding and misfolding mechanisms of the p53 DNA binding domain at physiological temperature. Protein Sci. 2006;15(11):2457-2465.
500. Blanden AR, Yu X, Loh SN, Levine AJ, Carpizo DR. Reactivating mutant p53 using small molecules as zinc metallochaperones: Awakening a sleeping giant in cancer. Drug Discov Today. 2015;20(11):1391-1397.
501. Hainaut P, Milner J. A structural role for metal ions in the "wild-type" conformation of the tumor suppressor protein p53. Cancer Res. 1993;53(8):1739-1742.
502. Puca R, Nardinocchi L, Porru M, Simon AJ, Rechavi G, Leonetti C, et al. Restoring p53 active conformation by zinc increases the response of mutant p53 tumor cells to anticancer drugs. Cell Cycle. 2011;10(10):1679-1689.
503. Jayaraman AK, Jayaraman S. Increased level of exogenous zinc induces cytotoxicity and up-regulates the expression of the ZnT-1 zinc transporter gene in pancreatic cancer cells. J Nutr Biochem. 2011;22(1):79-88.
504. Pucci D, Crispini A, Sanz Mendiguchía B, Pirillo S, Ghedini M, Morelli S, et al. Improving the bioactivity of Zn(II)-curcumin based complexes. Dalton Trans. 2013;42(26):9679-9687.
505. Garufi A, Trisciuoglio D, Porru M, Leonetti C, Stoppacciaro A, D'Orazi V, et al. A fluorescent curcumin-based Zn(II)-complex reactivates mutant (R175H and R273H) p53 in cancer cells. J Exp Clin Cancer Res. 2013;32(1):72.
506. Blanden AR, Yu X, Wolfe AJ, Gilleran JA, Augeri DJ, O'Dell RS, et al. Synthetic metallochaperone ZMC1 rescues mutant p53 conformation by transporting zinc into cells as an ionophore. Mol Pharmacol. 2015;87(5):825-831.
507. Maret W. Zinc in Cellular Regulation: The Nature and Significance of "Zinc Signals". Int J Mol Sci. 2017;18(11):2285.
508. Loh SN. The missing zinc: P53 misfolding and cancer. Metallomics. 2010;2(7):442-449.
509. Kumar S, Henning-Knechtel A, Magzoub M, Hamilton AD. Peptidomimetic-Based Multidomain Targeting Offers Critical Evaluation of Aβ Structure and Toxic Function. J Am Chem Soc. 2018;140(21):6562-6574.
510. Wu X, Hu Z, Nizzero S, Zhang G, Ramirez MR, Shi C, et al. Bone-targeting nanoparticle to co-deliver decitabine and arsenic trioxide for effective therapy of myelodysplastic syndrome with low systemic toxicity. J Control Release. 2017;268:92-101.
511. Bauer MR, Jones RN, Tareque RK, Springett B, Dingler FA, Verduci L, et al. A structure-guided molecular chaperone approach for restoring the transcriptional activity of the p53 cancer mutant Y220C. Future Med Chem. 2019;11(19):2491-2504.
512. Di Como CJ, Prives C. Human tumor-derived p53 proteins exhibit binding site selectivity and temperature sensitivity for transactivation in a yeast-based assay. Oncogene. 1998;16(19):2527-2539.
513. Wilcken R, Liu X, Zimmermann MO, Rutherford TJ, Fersht AR, Joerger AC, et al. Halogen-enriched fragment libraries as leads for drug rescue of mutant p53. J Am Chem Soc. 2012;134(15):6810-6818.
514. Stephenson Clarke JR, Douglas LR, Duriez PJ, Balourdas DI, Joerger AC, Khadiullina R, et al. Discovery of Nanomolar-Affinity Pharmacological Chaperones Stabilizing the Oncogenic p53 Mutant Y220C. ACS pharmacology & translational science. 2022;5(11):1169-1180.
515. Baud MGJ, Bauer MR, Verduci L, Dingler FA, Patel KJ, Horil Roy D, et al. Aminobenzothiazole derivatives stabilize the thermolabile p53 cancer mutant Y220C and show anticancer activity in p53-Y220C cell lines. Eur J Med Chem. 2018;152:101-114.
516. Boeckler FM, Joerger AC, Jaggi G, Rutherford TJ, Veprintsev DB, Fersht AR. Targeted rescue of a destabilized mutant of p53 by an in silico screened drug. Proc Natl Acad Sci U S A. 2008;105(30):10360-10365.
517. Liu X, Wilcken R, Joerger AC, Chuckowree IS, Amin J, Spencer J, et al. Small molecule induced reactivation of mutant p53 in cancer cells. Nucleic Acids Res. 2013;41(12):6034-6044.
518. Brundin P, Melki R, Kopito R. Prion-like transmission of protein aggregates in neurodegenerative diseases. Nat Rev Mol Cell Biol. 2010;11(4):301-307.
519. Geschwind MD. Prion Diseases. Continuum (Minneap Minn). Neuroinfectious Disease. 2015;21(6):1612-1638.
520. Eisenberg DS, Sawaya MR. Structural Studies of Amyloid Proteins at the Molecular Level. Annu Rev Biochem. 2017;86:69-95.
521. Chiti F, Dobson CM. Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu Rev Biochem. 2017;86:27-68.
522. Kim M, Kang J, Lee M, Han J, Nam G, Tak E, et al. Minimalistic Principles for Designing Small Molecules with Multiple Reactivities against Pathological Factors in Dementia. J Am Chem Soc. 2020;142(18):8183-8193.
523. Eisenberg D, Jucker M. The amyloid state of proteins in human diseases. Cell. 2012;148(6):1188-1203.
524. Wang G, Fersht AR. Propagation of aggregated p53: Cross-reaction and coaggregation vs. seeding. Proc Natl Acad Sci U S A. 2015;112(8):2443-2448.
525. Xu J, Reumers J, Couceiro JR, De Smet F, Gallardo R, Rudyak S, et al. Gain of function of mutant p53 by coaggregation with multiple tumor suppressors. Nat Chem Biol. 2011;7(5):285-295.
526. Silva JL, Cino EA, Soares IN, Ferreira VF, G APdO. Targeting the Prion-like Aggregation of Mutant p53 to Combat Cancer. Acc Chem Res. 2018;51(1):181-190.
527. Rangel LP, Costa DC, Vieira TC, Silva JL. The aggregation of mutant p53 produces prion-like properties in cancer. Prion. 2014;8(1):75-84.
528. Ano Bom AP, Rangel LP, Costa DC, de Oliveira GA, Sanches D, Braga CA, et al. Mutant p53 aggregates into prion-like amyloid oligomers and fibrils: Implications for cancer. J Biol Chem. 2012;287(33):28152-28162.
529. Silva JL, De Moura Gallo CV, Costa DC, Rangel LP. Prion-like aggregation of mutant p53 in cancer. Trends Biochem Sci. 2014;39(6):260-267.
530. Zhang WW, Li L, Li D, Liu J, Li X, Li W, et al. The First Approved Gene Therapy Product for Cancer Ad-p53 (Gendicine): 12 Years in the Clinic. Hum Gene Ther. 2018;29(2):160-179.
531. Parada LF, Land H, Weinberg RA, Wolf D, Rotter V. Cooperation between gene encoding p53 tumour antigen and ras in cellular transformation. Nature. 1984;312(5995):649-651.
532. Bischoff JR, Kirn DH, Williams A, Heise C, Horn S, Muna M, et al. An adenovirus mutant that replicates selectively in p53-deficient human tumor cells. Science. 1996;274(5286):373-376.

533. Rothmann T, Hengstermann A, Whitaker NJ, Scheffner M, zur Hausen H. Replication of ONYX-015, a potential anticancer adenovirus, is independent of p53 status in tumor cells. J Virol. 1998;72(12):9470-9478.
534. Goodrum FD, Ornelles DA. p53 status does not determine outcome of E1B 55-kilodalton mutant adenovirus lytic infection. J Virol. 1998;72(12):9479-9490.
535. Weinstein IB, Joe AK. Mechanisms of disease: Oncogene addiction–a rationale for molecular targeting in cancer therapy. Nat Clin Pract Oncol. 2006;3(8):448-457.
536. Eliyahu D, Raz A, Gruss P, Givol D, Oren M. Participation of p53 cellular tumour antigen in transformation of normal embryonic cells. Nature. 1984;312(5995):646-649.
537. Jenkins JR, Rudge K, Currie GA. Cellular immortalization by a cDNA clone encoding the transformation-associated phosphoprotein p53. Nature. 1984;312(5995):651-654.
538. Hainaut P, Milner J. Interaction of heat-shock protein 70 with p53 translated in vitro: Evidence for interaction with dimeric p53 and for a role in the regulation of p53 conformation. Embo J. 1992;11(10):3513-3520.
539. Hinds PW, Finlay CA, Frey AB, Levine AJ. Immunological evidence for the association of p53 with a heat shock protein, hsc70, in p53-plus-ras-transformed cell lines. Mol Cell Biol. 1987;7(8):2863-2869.
540. Peng Y, Chen L, Li C, Lu W, Chen J. Inhibition of MDM2 by hsp90 contributes to mutant p53 stabilization. J Biol Chem. 2001;276(44):40583-40590.
541. Li D, Marchenko ND, Schulz R, Fischer V, Velasco-Hernandez T, Talos F, et al. Functional inactivation of endogenous MDM2 and CHIP by HSP90 causes aberrant stabilization of mutant p53 in human cancer cells. Mol Cancer Res. 2011;9(5):577-588.
542. Blagosklonny MV, Toretsky J, Neckers L. Geldanamycin selectively destabilizes and conformationally alters mutated p53. Oncogene. 1995;11(5):933-939.
543. Whitesell L, Lindquist SL. HSP90 and the chaperoning of cancer. Nat Rev Cancer. 2005;5(10):761-772.
544. Shrestha L, Bolaender A, Patel HJ, Taldone T. Heat Shock Protein (HSP) Drug Discovery and Development: Targeting Heat Shock Proteins in Disease. Curr Top Med Chem. 2016;16(25):2753-2764.
545. Mahalingam D, Swords R, Carew JS, Nawrocki ST, Bhalla K, Giles FJ. Targeting HSP90 for cancer therapy. Br J Cancer. 2009;100(10):1523-1529.
546. Terzian T, Suh YA, Iwakuma T, Post SM, Neumann M, Lang GA, et al. The inherent instability of mutant p53 is alleviated by Mdm2 or p16INK4a loss. Genes Dev. 2008;22(10):1337-1344.
547. Ries S, Korn WM. ONYX-015: Mechanisms of action and clinical potential of a replication-selective adenovirus. British Journal of Cancer. 2002;86(1):5-11.
548. Hall AR, Dix BR, O'Carroll SJ, Braithwaite AW. p53-dependent cell death/apoptosis is required for a productive adenovirus infection. Nat Med. 1998;4(9):1068-1072.
549. Dix BR, O'Carroll SJ, Myers CJ, Edwards SJ, Braithwaite AW. Efficient induction of cell death by adenoviruses requires binding of E1B55k and p53. Cancer Res. 2000;60(10):2666-2672.
550. Garber K. China approves world's first oncolytic virus therapy for cancer treatment. J Natl Cancer Inst. 2006;98(5):298-300.
551. Kaelin WG Jr. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Cancer. 2005;5(9):689-698.
552. Li S, Topatana W, Juengpanich S, Cao J, Hu J, Zhang B, et al. Development of synthetic lethality in cancer: Molecular and cellular classification. Signal Transduction and Targeted Therapy. 2020;5(1):241.
553. Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017;355(6330):1152-1158.
554. Wang X, Simon R. Identification of potential synthetic lethal genes to p53 using a computational biology approach. BMC Med Genomics. 2013;6:30.
555. Moser R, Xu C, Kao M, Annis J, Lerma LA, Schaupp CM, et al. Functional kinomics identifies candidate therapeutic targets in head and neck cancer. Clin Cancer Res. 2014;20(16):4274-4288.
556. Hirai H, Arai T, Okada M, Nishibata T, Kobayashi M, Sakai N, et al. MK-1775, a small molecule Wee1 inhibitor, enhances anti-tumor efficacy of various DNA-damaging agents, including 5-fluorouracil. Cancer Biol Ther. 2010;9(7):514-522.
557. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L, Razak AR, et al. Phase I Study Evaluating WEE1 Inhibitor AZD1775 As Monotherapy and in Combination With Gemcitabine, Cisplatin, or Carboplatin in Patients With Advanced Solid Tumors. J Clin Oncol. 2016;34(36):4371-4380.
558. Guiley KZ, Shokat KM. A Small Molecule Reacts with the p53 Somatic Mutant Y220C to Rescue Wild-type Thermal Stability. Cancer Discov. 2023;13(1):56-69.
559. Liu JF, Xiong N, Campos SM, Wright AA, Krasner C, Schumer S, et al. Phase II Study of the WEE1 Inhibitor Adavosertib in Recurrent Uterine Serous Carcinoma. J Clin Oncol. 2021;39(14):1531-1539.
560. Horejs C. Organ chips, organoids and the animal testing conundrum. Nat Rev Mater. 2021;6(5):372-373.
561. Gavert N, Zwang Y, Weiser R, Greenberg O, Halperin S, Jacobi O, et al. Ex vivo organotypic cultures for synergistic therapy prioritization identify patient-specific responses to combined MEK and Src inhibition in colorectal cancer. Nat Cancer. 2022;3(2):219-231.
562. Awad MM, Liu S, Rybkin II, Arbour KC, Dilly J, Zhu VW, et al. Acquired Resistance to KRASG12C Inhibition in Cancer. N Engl J Med. 2021;384(25):2382-2393.
563. Canon J, Rex K, Saiki AY, Mohr C, Cooke K, Bagal D, et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. Nature. 2019;575(7781):217-223.
564. de Jonge M, de Weger VA, Dickson MA, Langenberg M, Le Cesne A, Wagner AJ, et al. A phase I study of SAR405838, a novel human double minute 2 (HDM2) antagonist, in patients with solid tumours. Eur J Cancer. 2017;76:144-151.
565. Bauer S, Demetri GD, Halilovic E, Dummer R, Meille C, Tan DSW, et al. Pharmacokinetic-pharmacodynamic guided optimisation of dose and schedule of CGM097, an HDM2 inhibitor, in preclinical and clinical studies. Br J Cancer. 2021;125(5):687-698.
566. Sallman DA, DeZern AE, Garcia-Manero G, Steensma DP, Roboz GJ, Sekeres MA, et al. Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant Myelodysplastic Syndromes. J Clin Oncol. 2021;39(14):1584-1594.
567. Cluzeau T, Sebert M, Rahmé R, Cuzzubbo S, Lehmann-Che J, Madelaine I, et al. Eprenetapopt Plus Azacitidine in TP53-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM). J Clin Oncol. 2021;39(14):1575-1583.

568. Mishra A, Tamari R, DeZern AE, Byrne MT, Gooptu M, Chen YB, et al. Eprenetapopt Plus Azacitidine After Allogeneic Hematopoietic Stem-Cell Transplantation for TP53-Mutant Acute Myeloid Leukemia and Myelodysplastic Syndromes. J Clin Oncol. 2022;40(34):3985-3993.
569. Park H, Shapiro GI, Gao X, Mahipal A, Starr J, Furqan M, et al. Phase Ib study of eprenetapopt (APR-246) in combination with pembrolizumab in patients with advanced or metastatic solid tumors. ESMO Open. 2022;7(5):100573.
570. Ray-Coquard I, Braicu I, Berger R, Mahner S, Sehouli J, Pujade-Lauraine E, et al. Part I of GANNET53: A European Multicenter Phase I/II Trial of the Hsp90 Inhibitor Ganetespib Combined With Weekly Paclitaxel in Women With High-Grade, Platinum-Resistant Epithelial Ovarian Cancer-A Study of the GANNET53 Consortium. Front Oncol. 2019;9:832.
571. Wang Y, Janku F, Piha-Paul S, Hess K, Broaddus R, Liu L, et al. Phase I studies of vorinostat with ixazomib or pazopanib imply a role of antiangiogenesis-based therapy for TP53 mutant malignancies. Sci Rep. 2020;10(1):3080.
572. Fu S, Hou MM, Naing A, Janku F, Hess K, Zinner R, et al. Phase I study of pazopanib and vorinostat: A therapeutic approach for inhibiting mutant p53-mediated angiogenesis and facilitating mutant p53 degradation. Ann Oncol. 2015;26(5):1012-1018.
573. Moore KN, Chambers SK, Hamilton EP, Chen LM, Oza AM, Ghamande SA, et al. Adavosertib with Chemotherapy in Patients with Primary Platinum-Resistant Ovarian, Fallopian Tube, or Peritoneal Cancer: An Open-Label, Four-Arm, Phase II Study. Clin Cancer Res. 2022;28(1):36-44.
574. Oza AM, Estevez-Diz M, Grischke EM, Hall M, Marmé F, Provencher D, et al. A Biomarker-enriched, Randomized Phase II Trial of Adavosertib (AZD1775) Plus Paclitaxel and Carboplatin for Women with Platinum-sensitive TP53-mutant Ovarian Cancer. Clin Cancer Res. 2020;26(18):4767-4776.
575. Rajurkar M, Parikh AR, Solovyov A, You E, Kulkarni AS, Chu C, et al. Reverse Transcriptase Inhibition Disrupts Repeat Element Life Cycle in Colorectal Cancer. Cancer Discov. 2022;12(6):1462-1481.
576. Issaeva N, Bozko P, Enge M, Protopopova M, Verhoef LG, Masucci M, et al. Small molecule RITA binds to p53, blocks p53-HDM-2 interaction and activates p53 function in tumors. Nat Med. 2004;10(12):1321-1328.
577. Sanz G, Singh M, Peuget S, Selivanova G. Inhibition of p53 inhibitors: Progress, challenges and perspectives. J Mol Cell Biol. 2019;11(7):586-599.
578. Graves B, Thompson T, Xia M, Janson C, Lukacs C, Deo D, et al. Activation of the p53 pathway by small-molecule-induced MDM2 and MDMX dimerization. Proc Natl Acad Sci U S A. 2012;109(29):11788-11793.
579. Wurz RP, Cee VJ. Targeted Degradation of MDM2 as a New Approach to Improve the Efficacy of MDM2-p53 Inhibitors. J Med Chem. 2019;62(2):445-447.
580. Kaar JL, Basse N, Joerger AC, Stephens E, Rutherford TJ, Fersht AR. Stabilization of mutant p53 via alkylation of cysteines and effects on DNA binding. Protein Sci. 2010;19(12):2267-2278.
581. Bauer MR, Joerger AC, Fersht AR. 2-Sulfonylpyrimidines: Mild alkylating agents with anticancer activity toward p53-compromised cells. Proc Natl Acad Sci U S A. 2016;113(36):E5271-E5280.
582. Zhang Q, Bergman J, Wiman KG, Bykov VJN. Role of Thiol Reactivity for Targeting Mutant p53. Cell Chem Biol. 2018;25(10):1219-1230. e3.
583. Punganuru SR, Madala HR, Venugopal SN, Samala R, Mikelis C, Srivenugopal KS. Design and synthesis of a C7-aryl piperlongumine derivative with potent antimicrotubule and mutant p53-reactivating properties. Eur J Med Chem. 2016;107:233-244.
584. Hiraki M, Hwang SY, Cao S, Ramadhar TR, Byun S, Yoon KW, et al. Small-Molecule Reactivation of Mutant p53 to Wild-Type-like p53 through the p53-Hsp40 Regulatory Axis. Chem Biol. 2015;22(9):1206-1216.
585. Gomes AS, Ramos H, Gomes S, Loureiro JB, Soares J, Barcherini V, et al. SLMP53-1 interacts with wild-type and mutant p53 DNA-binding domain and reactivates multiple hotspot mutations. Biochim Biophys Acta Gen Subj. 2020;1864(1):129440.
586. Soares J, Raimundo L, Pereira NA, Monteiro Â, Gomes S, Bessa C, et al. Reactivation of wild-type and mutant p53 by tryptophanolderived oxazoloisoindolinone SLMP53-1, a novel anticancer small-molecule. Oncotarget. 2016;7(4):4326-4343.
587. Gomes S, Bosco B, Loureiro JB, Ramos H, Raimundo L, Soares J, et al. SLMP53-2 Restores Wild-Type-Like Function to Mutant p53 through Hsp70: Promising Activity in Hepatocellular Carcinoma. Cancers (Basel). 2019;11(8):1151.
588. Demma M, Maxwell E, Ramos R, Liang L, Li C, Hesk D, et al. SCH529074, a small molecule activator of mutant p53, which binds p53 DNA binding domain (DBD):restores growth-suppressive function to mutant p53 and interrupts HDM2-mediated ubiquitination of wild type p53. J Biol Chem. 2010;285(14):10198-10212.
589. North S, Pluquet O, Maurici D, El-Ghissassi F, Hainaut P. Restoration of wild-type conformation and activity of a temperature-sensitive mutant of p53 (p53(V272M)) by the cytoprotective aminothiol WR1065 in the esophageal cancer cell line TE-1. Mol Carcinog. 2002;33(3):181-188.
590. Burmistrov V, Saxena R, Pitushkin D, Butov GM, Chung FL, Aggarwal M. Adamantyl Isothiocyanates as Mutant p53 Rescuing Agents and Their Structure-Activity Relationships. J Med Chem. 2021;64(10):6621-6633.
591. Tal P, Eizenberger S, Cohen E, Goldfinger N, Pietrokovski S, Oren M, et al. Cancer therapeutic approach based on conformational stabilization of mutant p53 protein by small peptides. Oncotarget. 2016;7(11):11817-11837.
592. Song B, Wang J, Ren Y, Su Y, Geng X, Yang F, et al. Butein inhibits cancer cell growth by rescuing the wild-type thermal stability of mutant p53. Biomed Pharmacother. 2023;163:114773.
593. Wang J, Zhao Q, Qi Q, Gu HY, Rong JJ, Mu R, et al. Gambogic acid-induced degradation of mutant p53 is mediated by proteasome and related to CHIP. J Cell Biochem. 2011;112(2):509-519.
594. Hu J, Cao J, Topatana W, Juengpanich S, Li S, Zhang B, et al. Targeting mutant p53 for cancer therapy: Direct and indirect strategies. J Hematol Oncol. 2021;14(1):157.
595. Proia DA, Bates RC. Ganetespib and HSP90: Translating preclinical hypotheses into clinical promise. Cancer Res. 2014;74(5):1294-1300.
596. Alexandrova EM, Yallowitz AR, Li D, Xu S, Schulz R, Proia DA, et al. Improving survival by exploiting tumour

dependence on stabilized mutant p53 for treatment. Nature. 2015;523(7560):352-356.
597. Krämer OH, Mahboobi S, Sellmer A. Drugging the HDAC6-HSP90 interplay in malignant cells. Trends Pharmacol Sci. 2014;35(10):501-509.
598. Parrales A, Ranjan A, Iyer SV, Padhye S, Weir SJ, Roy A, et al. DNAJA1 controls the fate of misfolded mutant p53 through the mevalonate pathway. Nat Cell Biol. 2016;18(11):1233-1243.
599. Paranjpe A, Srivenugopal KS. Degradation of NF-κB, p53 and other regulatory redox-sensitive proteins by thiol-conjugating and -nitrosylating drugs in human tumor cells. Carcinogenesis. 2013;34(5):990-1000.
600. Wang YL, Wu W, Su YN, Ai ZP, Mou HC, Wan LS, et al. Buxus alkaloid compound destabilizes mutant p53 through inhibition of the HSF1 chaperone axis. Phytomedicine. 2020;68:153187.
601. Zhang S, Zhou L, Hong B, van den Heuvel AP, Prabhu VV, Warfel NA, et al. Small-Molecule NSC59984 Restores p53 Pathway Signaling and Antitumor Effects against Colorectal Cancer via p73 Activation and Degradation of Mutant p53. Cancer Res. 2015;75(18):3842-3852.
602. Vakifahmetoglu-Norberg H, Kim M, Xia HG, Iwanicki MP, Ofengeim D, Coloff JL, et al. Chaperone-mediated autophagy degrades mutant p53. Genes Dev. 2013;27(15):1718-1730.
603. Kravchenko JE, Ilyinskaya GV, Komarov PG, Agapova LS, Kochetkov DV, Strom E, et al. Small-molecule RETRA suppresses mutant p53-bearing cancer cells through a p73-dependent salvage pathway. Proc Natl Acad Sci U S A. 2008;105(17):6302-6307.
604. Hong B, Prabhu VV, Zhang S, van den Heuvel AP, Dicker DT, Kopelovich L, et al. Prodigiosin rescues deficient p53 signaling and antitumor effects via upregulating p73 and disrupting its interaction with mutant p53. Cancer Res. 2014;74(4):1153-1165.
605. Khoo KH, Verma CS, Lane DP. Drugging the p53 pathway: Understanding the route to clinical efficacy. Nat Rev Drug Discov. 2014;13(3):217-236.
606. Batchelor E, Loewer A. Recent progress and open challenges in modeling p53 dynamics in single cells. Curr Opin Syst Biol. 2017;3:54-59.
607. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA, Knight R. The microbiome and human cancer. Science. 2021;371(6536):eabc4552.

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