

REVIEW

New insights into molecules and pathways of cancer metabolism and therapeutic implications

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Abbreviations: 1-MT, 1-methyl tryptophan; 2DG, 2-deoxyglucose; 3-BP, 3-bromopyruvate; AEA, endocannabinoids anandamide; AML, acute myeloid leukemia; AMPK, AMP-activated protein kinase; AR, adrenergic receptor; ASNase1, asparaginase 1; ASS1, argininosuccinate synthetase 1; AXIN, axis inhibition protein; BA, bile acid; BCAR4, breast cancer anti-estrogen resistance 4; CAC, colitis-associated cancer; CAD, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase; CAF, cancer-associated fibroblast; CCAR1, cell division cycle and apoptosis regulator protein 1; CKB, creatine kinase, brain-type; CRC, colorectal cancer; CRL, cullin-RING E3 ligase; CRP, C-reactive protein; CSC, cancer stem cell; CTP, citrate transporter protein; CUEDC2, CUE domain-containing protein 2; D2HG, D-2-hydroxyglutarate; DCA, deoxycholic acid; EDP, epoxydocosapentaenoic acid; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; ER, endoplasmic reticulum; ER α , estrogen receptor α ; EV, extracellular vesicle; FXR, farnesoid X receptor; G6PD, glucose-6-phosphate dehydrogenase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GBM, glioblastoma multiforme; GBTC, gallbladder and biliary tract cancer; Gln, glutamine; GLUT3, glucose transporter 3; GPT2, glutamic pyruvate transaminase 2; GR, glucocorticoid receptor; HCC, hepatocarcinoma; HCV, hepatitis C virus; H1SLA, HIF-1 α -stabilizing lncRNA; HK2, hexokinase 2; HMGCL, 3-hydroxy-3-methylglutaryl-CoA lyase; HMOX1, heme oxygenase 1; HMW, high-molecular-weight; HSP90, heat shock protein 90; IBD, intrahepatic bile duct; IDH, isocitrate dehydrogenase; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; IDO, indoleamine 2,3-dioxygenase; IL-6, interleukin-6; KDM8, lysine demethylase 8; KYN, kynurenine; LAPT4B, lysosomal protein transmembrane 4 beta; LDH, lactate dehydrogenase; LDHA, lactate dehydrogenase A; LIC, leukemia-initiating cell; lncRNA, long non-coding RNA; LSC, leukemia stem cell; lysoPC, lysophosphatidylcholine; MCT1, monocarboxylate transporter-1; MM, multiple myeloma; MPC, mitochondrial pyruvate carrier; mTOR, mammalian target of rapamycin; mTORC2, mTOR complex 2; NMDA, N-methyl-D-aspartic acid; NNMT, methyltransferase nicotinamide N-methyltransferase; NSCLC, non-small cell lung carcinoma; NSE, neuron-specific enolase; OOA, oxaloacetic acid; OXCT1, 3-oxoacid CoA-transferase 1; PCK1, phosphoenolpyruvate carboxykinase 1; PCK2, phosphoenolpyruvate carboxykinase 2; PDAC, pancreatic ductal adenocarcinoma; PDGFRA, platelet-derived growth factor receptor alpha; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; PDK2, pyruvate dehydrogenase kinase isozyme 2; PD-L1, programmed death-ligand 1; PEA, palmitylethanolamide; PEP, phosphoenolpyruvate; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4; PHD2, prolyl hydroxylase 2; PHGDH, phosphoglycerate dehydrogenase; pHGG, pediatric high-grade glioma; PI3K, phosphoinositide 3-kinase; PKB, protein kinase B; PKM2, pyruvate kinase M2; Plk1, polo-like kinase 1; PP1, protein phosphatase 1; PP2A, protein phosphatase 2A; PPAR, peroxisome proliferator-activated receptor; PPP, pentose phosphate pathway; PRMT5, protein arginine methyltransferase 5; PUMA, p53 upregulated modulator of apoptosis; R5P, ribose 5-phosphate; RIF1, replication timing regulatory factor 1; ROS, reactive oxygen species; SCC, squamous cell carcinoma; SDH, serine dehydratase; SIRT5, sirtuin5; SNS, sympathetic nervous system; SRC-3, steroid receptor coactivator-3; SREBP, serol regulatory element-binding protein; SRSF5, serine and arginine-rich splicing factor 5; STAT3-Socs3, signal transducers and activators of transcription 3-suppressor of cytokine signaling 3; TAM, tumor-associated macrophage; T-betaMCA, tauro-beta-muricholic acid; TCA, tricarboxylic acid; TFEB, transcription factor EB; TGF- β , transforming growth factor-beta; TIL, tumor-infiltrating T-lymphocyte; TKT, transketolase; TME, tumor microenvironment; Trp, tryptophan; UC, urea cycle; UGDH, UDP-glucose 6-dehydrogenase; VEGF, vascular endothelial growth factor; WTp53, wild-type p53; YAP, Yes-associated protein; ZIP14, ZRT- and IRT-like protein 14

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Abstract

Cancer cells are abnormal cells that can reproduce and regenerate rapidly. They are characterized by unlimited proliferation, transformation and migration, and can destroy normal cells. To meet the needs for cell proliferation and migration, tumor cells acquire molecular materials and energy through unusual metabolic pathways as their metabolism is more vigorous than that of normal cells. Multiple carcinogenic signaling pathways eventually converge to regulate three major metabolic pathways in tumor cells, including glucose, lipid, and amino acid metabolism. The distinct metabolic signatures of cancer cells reflect that metabolic changes are indispensable for the genesis and development of tumor cells. In this review, we report the unique metabolic alterations in tumor cells which occur through various signaling axes, and present various modalities available for cancer diagnosis and clinical therapy. We further provide suggestions for the development of anti-tumor therapeutic drugs.

KEYWORDS

cancer metabolism, metabolic pathway, metabolomic profiling, therapeutic implication

1 | INTRODUCTION

The Warburg effect (aerobic glycolysis) indicates that tumor cells prefer high-activity glycolysis to meet their survival demands [1]. However, until recently, this pathologic phenomenon has not been extensively researched and discussed. An epoch-making finding revealed that 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 (PFKFB4), a leading metabolic enzyme, activates glycolysis steroid receptor coactivator-3 (SRC-3) transcriptional activity and drives glucose flux towards the pentose phosphate pathway (PPP) functionally, which explains why tumors do not show active mitochondrial metabolic activity (Table 1) [2]. High tumor-associated glucose consumption frequently involves alterations at both molecular and cellular levels, which drive the malignant features of solid tumors. Thus, such metabolic pathways provide promising clinical targets.

Cancer cells possess multiple prime metabolic signaling pathways, sometimes re-routing glucose flux consumption to other metabolic pathways, which contributes to maintain an aerobic microenvironment in the tumor. For example, unlike proliferating leukemia cell populations that switch cellular respiration to aerobic glycolysis, oxidative phosphorylation, and proliferation pathways of leukemia stem cells (LSCs) are very reliant on amino acid metabolism [3]. We have previously reported that regulatory alterations of the metabolic network in cancer cells extend beyond the Warburg effect and individual metabolic flux. Thus, it is imperative to interrogate the

metabolome of tumors to elucidate the properties associated with clinical intervention. In this review, we summarize the unique metabolic alterations in tumor cells which occur through various signaling axes. Based on these metabolic alterations, we present various modalities available for cancer diagnosis and clinical therapy and further provide suggestions for the development of anti-tumor therapeutic drugs.

2 | GLUCOSE METABOLISM

2.1 | Phosphorylation

Phosphorylation is vital to coordinate cancer metabolism as well as the biosynthesis of cancer-related metabolites. Ma *et al.* [4] showed that the active dimer of polo-like kinase 1 (Plk1) and phosphorylated glucose-6-phosphate dehydrogenase (G6PD) caused sustained activation of the PPP and resulted in increased biosynthesis of macromolecules in HeLa cells (cervical cancer cells cultured *in vitro*) (Table 1). Additionally, the metabolic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) is highly regulated by phosphorylation. In breast cancer cells, it has been reported that prolongation of mitotic arrest causes AMP-activated protein kinase (AMPK)-dependent phosphorylation of PFKFB3, and thereby induce mitosis-associated translation. This results in an increase in glycolysis which replaces oxidative respiration in breast cancer (Table 1) [5].

TABLE 1 The functions of specific metabolic enzymes in cancer progression

Metabolic enzyme	Cancer type	Function	Reference
PFKFB4	Breast cancer	Activate the transcriptional activity of SRC-3 and drive the pentose phosphate pathway.	Dasgupta <i>et al.</i> , 2018 [2]
TRIM11		Sustain the ubiquitination of estrogen receptor α and metastasis behavior.	Tang <i>et al.</i> , 2020 [76]
PHGDH	Breast cancer	Decrease the integration with nucleotides of one-carbon units.	Pacold <i>et al.</i> , 2016 [91]
	Breast cancer Melanoma	Support tumorigenesis in serine-limited conditions.	Sullivan <i>et al.</i> , 2019 [89]
PCK2	Melanoma	PCK2 deletion regulates glucose metabolism and alleviates oxidative phosphorylation.	Luo <i>et al.</i> , 2017 [22]
HMGCL	Melanoma Leukemia	Respond to the MEK-ERK pathway and induce acetoacetate production.	Kang <i>et al.</i> , 2015 [63]
PCK1	Melanoma	Activate T cells to overexpress glycolytic phosphoenolpyruvate.	Ho <i>et al.</i> , 2015 [26]
	Hepatocarcinoma	Prevent INSIG1/2 from integrated with intracellular lipid and trigger sterol regulatory element-binding protein signaling.	Xu <i>et al.</i> , 2020 [60]
PFKFB3	Breast cancer	Trigger mitotic-associated translation and oxidative respiration.	Domenech <i>et al.</i> , 2015 [5]
	Cervical cancer	Prevent DNA from degradation and sustain glycolysis.	Li <i>et al.</i> , 2018 [11]
Plk1	Cervical cancer	Support the pentose phosphate pathway and increase macromolecules' biosynthesis.	Ma <i>et al.</i> , 2017 [4]
G6PD	Osteosarcoma	Trigger NADPH and ribose synthesis and attenuated reactive oxygen species.	Du <i>et al.</i> , 2013 [52]
ASNase1		Allow conversion between asparagine and aspartate.	Sullivan <i>et al.</i> , 2018 [99]
UGDH	Lung cancer	Induce epithelial-mesenchymal transition and metastatic growth.	Wang <i>et al.</i> , 2019 [6]
GAPDH		Respond to glucose signal.	Li <i>et al.</i> , 2014 [12]
PP1		Dephosphorylate axis inhibition protein and stimulate Wnt/ β -catenin signaling.	Mei <i>et al.</i> , 2018 [71]
HMOX1		Stabilize Bach1 and support metastasis.	Lignitto <i>et al.</i> , 2019 [126]
CKB	Colorectal cancer	Induce liver-colonization.	Loo <i>et al.</i> , 2015 [7]
GLUD1		Facilitate glutamine to be incorporated into the tricarboxylic acid cycle.	Wang <i>et al.</i> , 2018 [79]
GPT2	Colon cancer	Regulate glutamine catabolism.	Smith <i>et al.</i> , 2016 [80]
HK2	Lung cancer	Promote the Warburg effect.	Kim <i>et al.</i> , 2019 [25]
	Glioblastoma	Impair central nervous system with activated glycolysis and mitochondrial translocation	Wolf <i>et al.</i> , 2011 [13]
Cdc25A	Glioblastoma	Sustain glycolysis.	Liang <i>et al.</i> , 2016 [9]
IDH1 mutant	Glioblastoma/glioma	Impair chromosomal topology and activate platelet-derived growth factor receptor alpha.	Flavahan <i>et al.</i> , 2016 [42]
		Induce D2HG production to trigger neuronal activity.	Chen <i>et al.</i> , 2017 [43]
		Alleviate pyruvate dehydrogenase phosphorylation, upregulate HIF-1 and pyruvate dehydrogenase kinase-3, and induce glutamate generation.	Izquierdo-Garcia <i>et al.</i> , 2015 [45]

(Continues)

TABLE 1 (Continued)

Metabolic enzyme	Cancer type	Function	Reference
PKM2	Ovarian cancer	Control glycolytic rate.	Chao <i>et al.</i> , 2017 [14]
Methyltransferase nicotinamide N-methyltransferase		Induce cancer-associated fibroblast phenotype alterations and cause depletion of S-adenosyl methionine.	Eckert <i>et al.</i> , 2019 [95]
PDK2	Leukemia	Regulate glycolysis, home leukemia-initiating cells, and trigger symmetric cell division.	Hao <i>et al.</i> , 2019 [15]
KDM8	Prostate cancer	Interact with pyruvate kinase M2 and modulate glycolytic gene activities under hypoxic conditions.	Wang <i>et al.</i> , 2019 [17]
CAD	Prostate cancer Lung cancer Breast cancer	Induce both pyrimidine synthesis and transversion mutations at the nucleic acid and protein levels.	Lee <i>et al.</i> , 2018 [116]
LDHA	Hepatocarcinoma	Modulate aerobic glycolysis.	Zhong <i>et al.</i> , 2017 [16]
PDK1		Regulate the tricarboxylic acid cycle in hypoxia-inducible factor-1 independent pathway.	Ma <i>et al.</i> , 2014 [18]
PRMT5		Activate the sterol regulatory element-binding protein methylation and lipogenesis.	Liu <i>et al.</i> , 2016 [59]
OXCT1		Drive ketone metabolism to the tricarboxylic acid cycle and inactivate AMP-activated protein kinase.	Huang <i>et al.</i> , 2016 [62]
TKT		Regulate R5P expression and nucleotide synthesis.	Li <i>et al.</i> , 2019 [51]
P5C synthase and P5C reductase 1	Kidney cancer Prostate cancer Burkitt lymphoma	Direct proline biosynthesis from glutamine.	Liu <i>et al.</i> , 2012 [82]
Cytochrome c oxidase	Pancreatic cancer	Mediate oxidative phosphorylation and ATP production.	Ishida <i>et al.</i> , 2013 [114]
SDH		Induce pyruvate production.	Yu <i>et al.</i> , 2019 [90]
PP2A	Gastric cancer	Target MST1/2, trigger YAP signaling and suppress the Hippo tumor suppressor with the regulatory subunit, STRN3.	Tang <i>et al.</i> , 2020 [73]
CRLs	Colitis-associated cancer	Induce ST7 ubiquitination in an inflammatory tumor microenvironment.	Liu <i>et al.</i> , 2019 [77]
IDO	Multiple myeloma	Block T cells and decrease antitumor bioactive substances production.	Yan <i>et al.</i> , 2019 [101]
LDH	Squamous cell carcinoma	LDH defectiveness sustains glycolysis.	Flores <i>et al.</i> , 2019 [33]

Abbreviations: ASNase1, asparaginase 1; CAD, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase; CKB, creatine kinase, brain-type; CRL, cullin-RING E3 ligase; G6PD, glucose-6-phosphate dehydrogenase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GLUT1, glutamate dehydrogenase 1; GPT2, glutamic pyruvate transaminase 2; HK2, hexokinase 2; HMGCL, 3-hydroxy-3-methylglutaryl-CoA lyase; HMOX1, heme oxygenase 1; IDH1, isocitrate dehydrogenase 1; IDO, indoleamine 2,3-dioxygenase; KDM8, lysine demethylase 8; LDH, isocitrate dehydrogenase.; LDHA, lactate dehydrogenase A; OXCT1, 3-oxoacid CoA-transferase 1; PCK1, phosphoenolpyruvate carboxykinase 1; PCK2, phosphoenolpyruvate carboxykinase 2; PDK1, pyruvate dehydrogenase kinase 1; PDK2, pyruvate dehydrogenase kinase isozyme 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4; PHGDH, phosphoglycerate dehydrogenase; PKM2, pyruvate kinase M2; Plk1, polo-like kinase 1; PPI, protein phosphatase 1; PP2A, protein phosphatase 2A; PRMT5, protein arginine methyltransferase 5; SDH, serine dehydratase; TKT, transketolase; TRIM11, tripartite motif containing 11; UGDH, UDP-glucose 6-dehydrogenase.

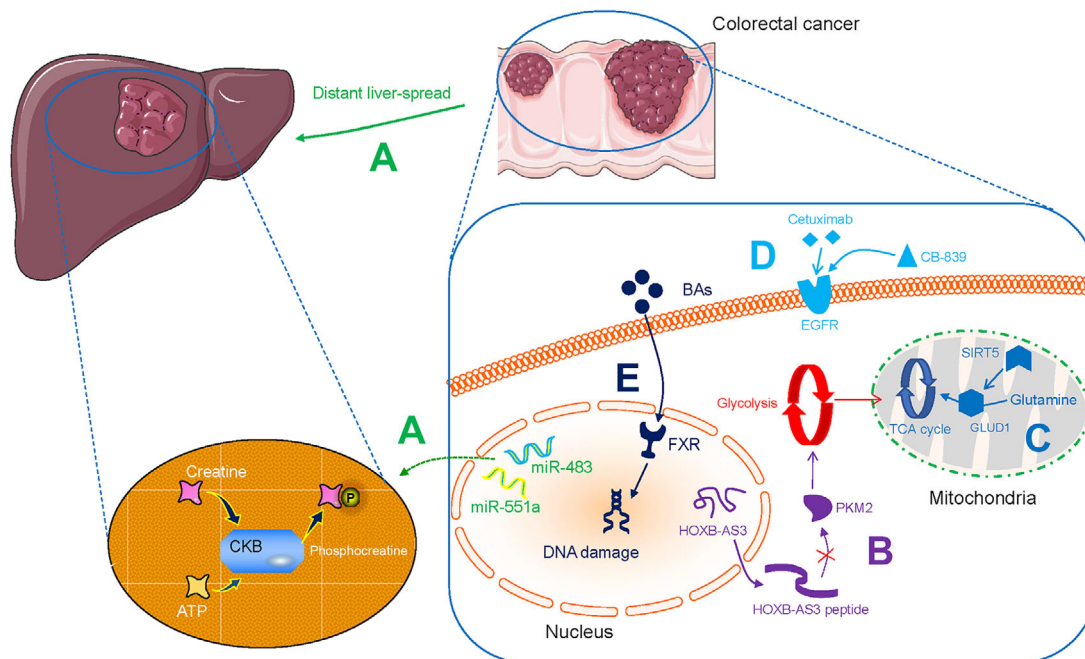


FIGURE 1 Metabolic alterations in colorectal cancer. A. miR-551a and miR-483 induce CKB-directed creatine phosphorylation and ATP-sustaining liver colonization. B. LncRNA HOXB-AS3-encoded peptide alleviates the formation of PKM2 and downregulates glycolysis. C. SIRT5 activates GLUD1 and facilitates Gln to be incorporated into the TCA cycle. D. EGFR-targeted cetuximab in combination with CB-839 can improve therapeutic efficacy. E. BAs impair intestinal FXR and induce subsequent DNA damage. Abbreviations: CKB, creatine kinase brain-type; LncRNA, long non-coding RNA; PKM2, pyruvate kinase M2; SIRT5, sirtuin5; GLUD1, glutamate dehydrogenase 1; Gln, glutamine; TCA, tricarboxylic acid; EGFR, epidermal growth factor receptor; BA, bile acid; FXR, farnesoid X receptor;

Phosphorylation often accelerates cancer invasion and metastasis. Wang *et al.* [6] found that the activation of epidermal growth factor receptor (EGFR) in metastatic lung cancer induced the phosphorylation of UDP-glucose 6-dehydrogenase (UGDH) at tyrosine 473 and stimulated the expression of SNAI1 mRNA; activated EGFR also promoted epithelial-mesenchymal transition (EMT) (Table 1). Loo *et al.* [7] identified multiple miRNAs, including miR-551a and miR-483, which stimulated creatine kinase, brain-type (CKB) and thereby induced the phosphorylation of creatine to produce phosphocreatine, leading to sustained ATP production and the colonization of colorectal cancer (CRC) cells in the liver (Table 1 and Figure 1A).

Phosphorylation is also associated with converting physiological signaling factors to cancer-promoting factors. Kim *et al.* [8] showed that the nuclear oncogenic wild-type p53 (WTP53) downregulated pyruvate-directed oxidative phosphorylation by triggering a p53 upregulated modulator of apoptosis (PUMA)-inactivated mitochondrial pyruvate carrier (MPC) in hepatocarcinoma (HCC; Figure 2A). Liang *et al.* [9] discovered that the phosphatase Cdc25A is activated by phosphorylation at Y59 by EGFR-c-Src signaling, and regulates the cell cycle. They further demonstrated that the activated Cdc25A sustains glycolysis and is related to the grades of human glioblastoma malig-

nancy (Table 1). Phosphorylation-dependent networks cause metabolic abnormalities and instigate malignancies, and thus can be explored to identify potential therapeutic targets.

2.2 | Acetylation

Acetylation of various targets promotes cancer development and is thought to occur as a response to glucose consumption. Chen *et al.* [10] discovered that serine and arginine-rich splicing factor 5 (SRSF5) was hyperacetylated in lung carcinoma, blocked Smurf1-coordinated ubiquitylation, sustained the splicing of cell division cycle and apoptosis regulator protein 1 (CCAR1), and responded to increased acetyl CoA biosynthesis and upregulated glucose consumption. Li *et al.* [11] demonstrated that cisplatin triggered the acetylation of accumulated PFKFB3 in the cytoplasm, contributing to the prevention of DNA degradation in glycolytic HeLa cells (Table 1). Li *et al.* [12] proposed that acetylation at lysine 254 increased glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity, and responded to intracellular glucose consumption in lung cancer (Table 1). Therefore, acetylation significantly supports cancer cell proliferation and aggressive invasion.

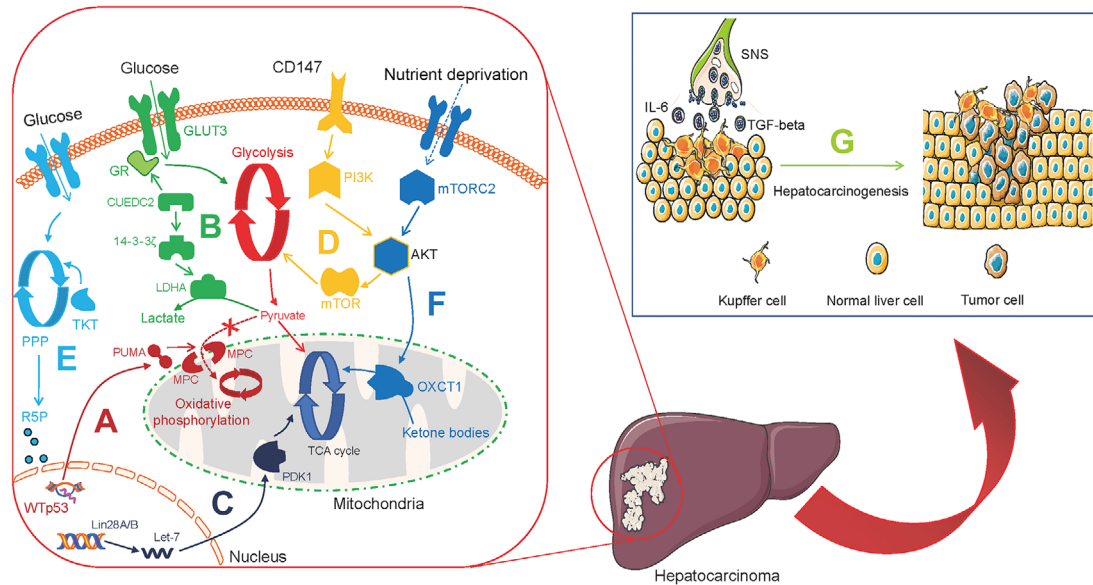


FIGURE 2 Metabolic alterations in hepatocarcinoma. A. WTP53 downregulates pyruvate-directed oxidative phosphorylation by triggering PUMA-inactivated MPC. B. CUEDC2 triggers the GR-GLUT3 peptide axis and 14-3-3 ζ -LDHA pathway to produce lactate. C. Lin28A and Lin28B express aberrantly while let-7 downregulates, which contributes to activate PDK1 to TCA cycle. D. CD147 sustains the Warburg effect through PI3K/Akt/mTOR axis. E. TKT activates R5P and subsequent nucleotide production. F. mTORC2-AKT axis triggers OXCT1 to drive ketolysis to the TCA cycle and inactivate AMPK. G. SNS regulates liver inflammation and secretory IL-6 and TGF- β production to trigger hepatocarcinogenesis. Abbreviations: WTP53, wild-type p53; PUMA, p53 upregulated modulator of apoptosis; MPC, mitochondrial pyruvate carrier; CUEDC2, CUE domain-containing protein 2; GR, glucocorticoid receptor; GLUT3, glucose transporter 3; LDHA, lactate dehydrogenase A; PDK1, pyruvate dehydrogenase kinase 1; TCA, tricarboxylic acid; TKT, transketolase; R5P, ribose 5-phosphate; PPP, pentose phosphate pathway; mTORC2, mTOR complex 2; OXCT1, 3-oxoacid CoA-transferase 1; AMPK, AMP-activated protein kinase; SNS, sympathetic nervous system; IL-6, interleukin-6; TGF- β , transforming growth factor-beta

2.3 | Enzyme catalysis

Aberrant overexpression of glycolysis-associated enzymes in tumor tissue is common and is associated with the Warburg effect. In human glioblastoma multiforme (GBM), hexokinase 2 (HK2) promotes the migration of chemotherapy-resistant GBM cells into the central nervous system, this effect is associated with protein kinase B (PKB)-stimulated glycolysis and mitochondrial translocation (Table 1) [13]. In ovarian cancer, pyruvate kinase M2 (PKM2) has been shown to control glycolytic rate (Table 1) [14]. In leukemia, pyruvate dehydrogenase kinase isozyme 2 (PDK2) in the bone marrow regulates the levels of glycolysis and recruits leukemia-initiating cells (LICs), which triggers symmetric cell division (Table 1) [15]. Multiple glycolysis enzymes jointly coordinate the Warburg effect. For example, Zhong *et al.* [16] proposed that the CUE domain-containing protein 2 (CUEDC2) is regulated by the glucocorticoid receptor (GR)-glucose transporter 3 (GLUT3) peptide axis as well as the 14-3-3 ζ -lactate dehydrogenase A (LDHA) pathway, and promotes the conversion of pyruvate to be converted to lactate in HCC (Table 1, Figure 2B and Figure 3).

Furthermore, the concentration of oxygen in the tumor microenvironment (TME) affects glycolytic enzymes indirectly. Wang *et al.* [17] found that the histone lysine demethylase lysine demethylase 8 (KDM8) interacts with PKM2 and subsequently modulates hypoxia-inducible factor-1 alpha (HIF-1 α) to upregulate glycolytic gene activities in prostate cancer cells under hypoxic conditions (Table 1). Furthermore, Ma *et al.* [18] reported that aberrantly expressed Lin28A and Lin28B and decreased let-7 results in upregulating pyruvate dehydrogenase kinase 1 (PDK1) in the HIF-1 independent pathway and modulating tricarboxylic acid (TCA) cycle in the aerobic tumor environment of HCC (Table 1 and Figure 2C). Proliferating tumors enable the Warburg effect in both ambient oxygen levels and in the anaerobic TME via glycolytic-associated genes and enzymes. Previously, this aspect has received little attention.

2.4 | Glycolysis and long non-coding RNAs (lncRNAs)

lncRNAs are RNA molecules that are not translated into proteins. However, they regulate the metabolic

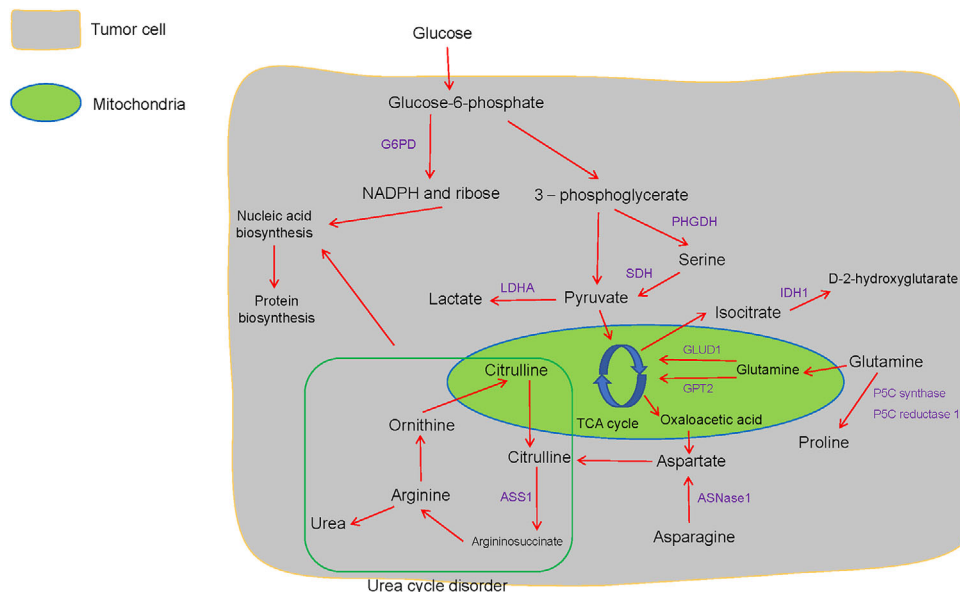


FIGURE 3 The correlation between glucose metabolism and amino acid metabolism in tumor cells. Aerobic glycolysis contributes to serine metabolism, and glutamine metabolism and Warburg effect transmit precursors to the TCA cycle. Arginine is cleaved to produce urea and ornithine. Ornithine supports citrulline biosynthesis in the mitochondria, and subsequently to arginine renewal, and this series of reactions is termed as the urea cycle. And the urea cycle disorder and pentose phosphate pathway alter nucleic acid level. Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; PHGDH, phosphoglycerate dehydrogenase; SDH, serine dehydratase; LDHA, lactate dehydrogenase A; IDO, indoleamine 2,3-dioxygenase; IDH1, isocitrate dehydrogenase 1; GLUD1, glutamate dehydrogenase 1; GPT2, glutamic pyruvate transaminase 2; ASNase1, asparaginase 1; ASS1, argininosuccinate synthetase 1

characteristics of cancers such as CRC. Tang *et al.* [19] discovered that in CRC cells, upregulated lncRNA GLCC1 in conditions of glucose depletion protected the ubiquitination of c-MYC transcriptional factor by integration with heat shock protein 90 (HSP90). In addition, the peptides encoded by lncRNAs are involved in regulating metabolism in CRC tumor cells. The lncRNA, HOXB-AS3-encoded peptide (HOXB-AS3 peptide) inhibited the expression of PKM2 and downregulated glycolysis, suggesting that HOXB-AS3 peptide deficiency is a critical oncogenic event in CRC (Figure 1B) [20]. Zheng *et al.* [21] found that Yes-associated protein (YAP)-upregulated lncRNA breast cancer anti-estrogen resistance 4 (BCAR4), coordinated Hedgehog signaling and enhanced the transcription of HK2 and PFKFB3 to generate secretory lactate (Figure 4A). These observations not only validate lncRNAs as regulators of tumors with potential clinical value but also reveal regulatory mechanisms for controlling tumors proliferation and energy metabolism.

2.5 | Glycolysis and mitochondria

The unique metabolic profile of cancer cells is characterized by suppressed mitochondrial glucose oxidation. Luo *et al.* [22] demonstrated that reduced mitochondrial phosphoenolpyruvate carboxykinase 2 (PCK2) led to

glucose carbon flow via oxaloacetic acid (OOA)-malate-pyruvate and acetyl-CoA-fatty acid axis and suppressed the oxidative phosphorylation in melanoma (Table 1). Altered mitochondrial metabolism is a crucial factor in pediatric high-grade gliomas (pHGGs). Shen *et al.* [23] found that dichloroacetate can stimulate mitochondrial oxidation and reduce the Warburg effect, and consequently interrupt the metabolism of tumor cells (Table 2). Reversing mitochondrial oxidation suppression holds promise in metabolic oncology.

2.6 | Glycolysis and T-cell

It is acknowledged that aerobic glycolysis restricts T-cell-mediated tumoricidal effector functions. Li *et al.* [24] reported that CD147 sustained the Warburg effect in HCC through the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) axis, which is correlated with T-cell immunosuppression (Figure 2D). Kim *et al.* [25] found that programmed death-ligand 1 (PD-L1) triggered HK2 to promote the Warburg effect in non-small cell lung carcinoma (NSCLC), a low expression of CD8⁺ T-cell function-associated genes was noted (Figure 5A and Table 1). However, aerobic glycolysis promotes effector T-cells from immunopathological impairments triggered by the TME. Ho *et al.*

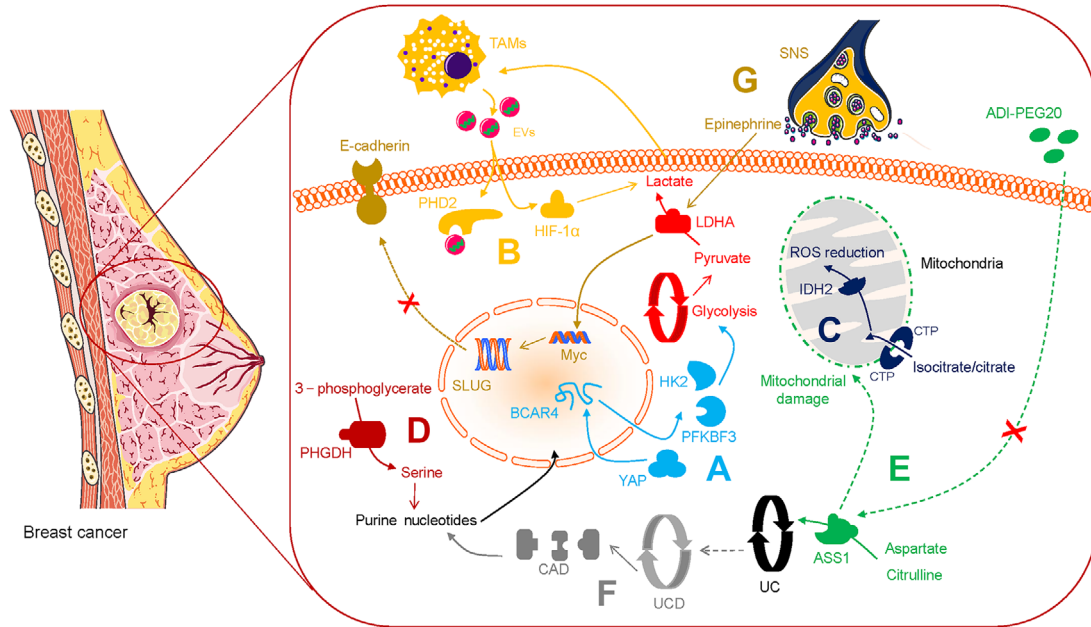


FIGURE 4 Metabolic alterations in breast cancer. A. YAP-upregulated lncRNA BCAR4 enhances the transcription of HK2 and PFKFB3 to generate lactate. B. TAM-derived EVs deliver HISLA, which antagonizes the binding of PHD2 and HIF-1 α . C. Isocitrate/citrate enters the mitochondria via CTP and enables ROS stress downregulation. D. PHGDH improves serine levels and sustains purine and nucleotides biosynthesis. E. ADI-PEG20 induces ASS1 deprivation and attenuates arginine synthesis with mitochondrial damage. F. UC disorder activates CAD and contributes to subsequent nucleic acid synthesis. G. SNS releases epinephrine to trigger LDHA and stabilize Myc, subsequently triggers SLUG and inactivates E-cadherin. Abbreviations: YAP, Yes-associated protein; lncRNA, long non-coding RNA; BCAR4, breast cancer anti-estrogen resistance 4; HK2, hexokinase 2; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; TAM, tumor-associated macrophage; EV, extracellular vesicle; HISLA, HIF-1 α -stabilizing lncRNA; PHD2, prolyl hydroxylase 2; HIF-1 α , hypoxia-inducible factor-1 alpha; CTP, citrate transporter protein; ROS, reactive oxygen species; IDH2, isocitrate dehydrogenase 2; PHGDH, phosphoglycerate dehydrogenase; ADI-PEG20, pegylated arginine deiminase; ASS1, argininosuccinate synthetase 1; UC, urea cycle; CAD, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase; SNS, sympathetic nervous system; LDHA, lactate dehydrogenase A

[26] validated that T-cells overexpressed the glycolytic metabolite phosphoenolpyruvate (PEP) in melanoma via phosphoenolpyruvate carboxykinase 1 (PCK1) activity, which bolstered T-cell functions (Table 1). Further exploration of metabolic checkpoints for T-cells could contribute to the elucidation of new forms of tumor immunity.

2.7 | Glycolysis and macrophage

The TME contains abundant infiltrating immune cells, including tumor-associated macrophages (TAMs) [27]. Chen *et al.* [28] reported that to sustain the Warburg effect in breast cancer, extracellular vesicles (EVs) delivered HIF-1 α -stabilizing lncRNA (HISLA), which antagonized the binding of prolyl hydroxylase 2 (PHD2) to HIF-1 α to stabilize HIF-1 α (Figure 4B). This consequently led TAM to sustain aerobic glycolysis and exhibit anti-apoptotic ability, while secretory lactate remarkably upregulated HISLA in TAMs reciprocally. In addition, metastatic lung adenocarcinoma-derived

lactate stimulated mTORC1/transcription factor EB (TFEB)/ATP6V0d2/HIF-2 α and promoted the expression of vascular endothelial growth factor (VEGF) [29]. Within the TME, altered TAMs acquire invasive properties which can be correlated with aerobic glycolysis.

2.8 | Glycolysis and cancer stem cell (CSC)

CSCs possess self-renewal properties and the capability to differentiate into various tumor cell subpopulations [30]. Due to the Warburg effect, a high level of glucose depletion is observed in the TME. Tumor cells tend to increase stem cells phenotype to adapt to microenvironmental changes [31]. Significantly, the Warburg effect is implicated in the invasive activity of CSCs. Luo *et al.* [32] validated the critical role of breast CSCs, and showed that in these cells glycolysis was active while under dormancy, whereas antioxidant responses were exhibited in the proliferating state. These observations suggest that the metabolic vulnerabilities of CSCs may provide novel ways to target cancer cells.

TABLE 2 Anti-tumor effectors in targeting cancer metabolism

Anti-tumor effector	Molecular mechanism	Reference
Dichloroacetate	Reduce the Warburg effect.	Shen <i>et al.</i> , 2020[23]
2DG	Combining 2DG with rapamycin inhibits glycolysis.	Zhao <i>et al.</i> , 2016 [37]
Clomifene	Induce mutant enzyme downregulations and occupy the allosteric site of mutations.	Zheng <i>et al.</i> , 2017 [47]
Enasidenib	Enhance molecular remissions and mitigate hematopoietic differentiation damage in acute myeloid leukemia.	Stein <i>et al.</i> , 2019 [48]
AGI-5198	Decrease D2HG, inhibit metastasis, impair cell cycling, and activate apoptosis in chondrosarcoma.	Li <i>et al.</i> , 2015 [49]
Polydatin	Act as glucose-6-phosphate dehydrogenase inhibition and block pentose phosphate pathway.	Mele <i>et al.</i> , 2018 [54]
EDPs	Block angiogenesis as well as endothelial cell transmission and vascular endothelial growth factor receptor 2-induced protease generation.	Zhang <i>et al.</i> , 2013 [68]
Hakai	Inhibit E-cadherin ubiquitination and suppress EMT	Martinez-Iglesias <i>et al.</i> , 2020 [78]
CB-839	Improve therapeutic efficacy in cetuximab-resistant colorectal cancer.	Cohen <i>et al.</i> , 2020 [86]
	Combining arsenic trioxide or homoharringtonine with CB-839 decreases glutathione synthesis and upregulate mitochondrial reactive oxygen species	Gregory <i>et al.</i> , 2019 [87]
1-MT	Improve the therapeutic efficacy of Doxorubicin in cancer treatment.	Lan <i>et al.</i> , 2020 [102]
ADI-PEG20	Induce argininosuccinate synthetase deprivation.	Huang <i>et al.</i> , 2013 [104]
	Be sensitive to prostate cancer cells with mitigated argininosuccinate synthetase and suppress early protective autophagy.	Kim <i>et al.</i> , 2009 [105]
	Induce autophagy-dependent death of breast cancer cells with the loss of argininosuccinate synthetase 1.	Qiu <i>et al.</i> , 2014 [106]
Vitamin D/25-hydroxyvitamin D	Decrease the risk of colorectal cancer and induce an immune response.	Song <i>et al.</i> , 2016 [110, 111]
	Promote T-cell function and decrease inflammation of tumor microenvironment in breast cancer.	Karkeni <i>et al.</i> , 2019 [112]
Propranolol	Synergize with anti-cancer vaccine in cancer immunotherapies	Daher <i>et al.</i> , 2019 [123]

Abbreviations: 2DG, 2-deoxyglucose; EDP, epoxydocosapentaenoic acid; EMT, epithelial-mesenchymal transition.

2.9 | Glycolysis and lactate metabolism

Recently many approaches have been attempted to target the Warburg effect, though valid therapeutic outcomes were not achieved. Flores *et al.* [33] reported that squamous cell carcinoma (SCC) cells with defective activity of lactate dehydrogenase (LDH) showed decreased glucose uptake and glycolytic metabolite production (Table 1). It is possible that tumorigenesis does not require active aerobic glycolysis, which overrides the dogma that tumors must rely on high glucose metabolically. Faubert *et al.* [34] provided evidence to prove that compared with glucose, lactate was the dominant carbon source for the TCA cycle in NSCLC, and was transported using the monocarboxylate transporter-1 (MCT1; Figure 5B). Hensley *et al.*

[35] observed and further identified the value of lactate as an available non-glucose carbon source in well-perfused tumor areas. These studies strongly indicate that tumors can use lactate as a fuel *in vivo*, and may not rely exclusively on aerobic glycolysis.

2.10 | The promise of glucose metabolism-glycolysis inhibition

Targeting aerobic glycolysis has become a promising chemotherapeutic strategy in the clinic. The glycolysis inhibitor 2-deoxyglucose (2DG) is a potent anti-cancer agent, and can function as an adjuvant drug in chemotherapy [36]. Zhao *et al.* [37] reported that rapamycin inhibited

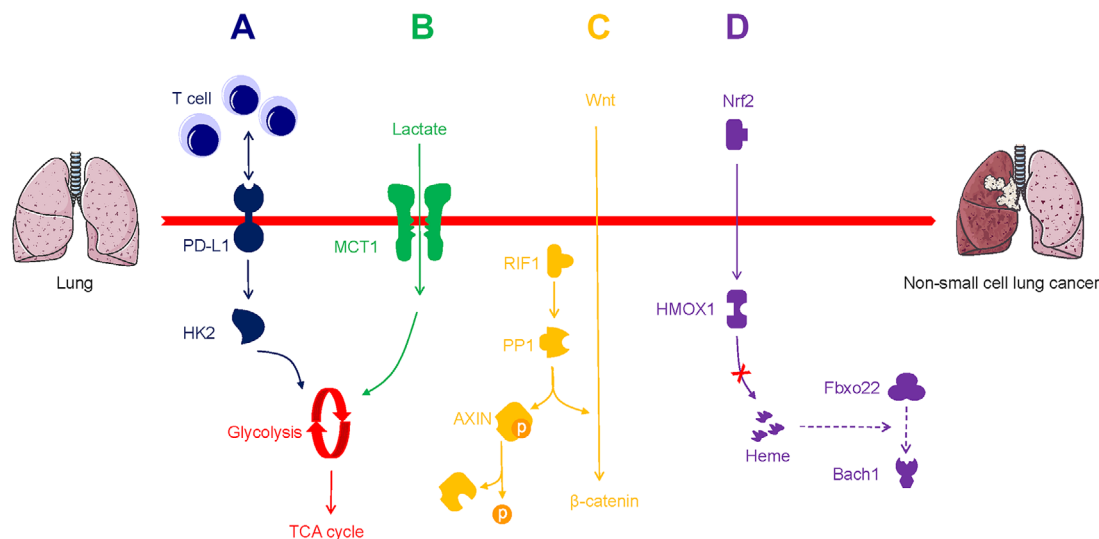


FIGURE 5 Metabolic alterations in non-small cell lung cancer progression and metastasis. A. PD-L1 triggers HK2 to promote the Warburg effect with immunosuppression. B. Lactate is driven to the TCA cycle via MCT1. C. PP1 to dephosphorylate AXIN and stimulates Wnt/ β -catenin axis. D. Nrf2 suppresses the heme-induced and Fbxo22-induced degradation of Bach1 through HMOX1. Abbreviations: PD-L1, programmed death-ligand 1; HK2, hexokinase 2; TCA, tricarboxylic acid; MCT1, monocarboxylate transporter-1; PP1, RIF1 triggers protein phosphatase 1; AXIN, axis inhibition protein; HMOX1, heme oxygenase 1

mTORC1 with LDHA downregulation, and the combination of rapamycin with 2DG potently influenced glycolysis in malignancies (Table 2). Nonetheless, glycolysis inhibitors including 2DG have not been used in clinical applications owing to nonspecific distribution to tumor tissue, and low bioavailability. Dong *et al.* [38] developed a nanoplatform that could target cancer cells and further modulate the TME based on photodynamic therapy and 2DG-triggered endoplasmic reticulum (ER) stress. Zhang *et al.* [39] designed a liposomal nanocarrier that readily transmitted 3-bromopyruvate (3-BP), another glycolysis inhibitor, into cancer cells without distinct side effects. Delivering glycolysis inhibitors using nanoscale functional materials represents a crucial step forward in the precise treatment of malignancies.

2.11 | Mutant isocitrate dehydrogenase (IDH)-dependent pathway

Previously, an isocitrate dehydrogenase 1 (*IDH1*) mutant subset was reported in prostate cancer [40]. Cytosolic *IDH* mutations that convert isocitrate into D-2-hydroxyglutarate (D2HG) initiate events that allow primary clinical detection and prognosis prediction in gliomas (Figure 3) [41]. Flavahan *et al.* [42] identified *IDH* mutants that contribute to gliomagenesis via impaired chromosomal topology and trigger activities of the platelet-derived growth factor receptor alpha (*PDGFRA*) oncogene (Table 1). Chen *et al.* [43] discovered that D2HG induced

neuronal activity by simulating the binding of glutamate to the N-methyl-D-aspartic acid (NMDA) receptor, and indicated that the *IDH1* mutant caused a high risk of seizures in glioma patients (Table 1). Jiang *et al.* [44] reported that isocitrate/citrate could enter the mitochondria via the citrate transporter protein (CTP), this metabolite was involved in isocitrate dehydrogenase 2 (*IDH2*)-induced oxidation, resulting in NADPH production, reactive oxygen species (ROS) stress downregulation, and stabilized the TME in lung, colon, and breast cancer (Figure 4C). Also, Izquierdo-Garcia *et al.* [45] proposed that *IDH1* mutations inhibited the pyruvate dehydrogenase (PDH) phosphorylation, upregulated HIF-1 and pyruvate dehydrogenase kinase-3 in glioblastoma cells, and reprogrammed pyruvate metabolism to aid glutamate generation (Table 1).

Significantly, Okoye-Okafor *et al.* [46] revealed that inhibitors of mutant *IDH1* contributed to D-2HG reduction, myeloid differentiation, and granulocytic differentiation regulated by precursor cells in acute myeloid leukemia (AML). Zheng *et al.* [47] also showed that clomifene, an *IDH1* mutant inhibitor, occupied the allosteric site of mutations in a dose-dependent non-competitive manner, and led to the downregulation of the mutant enzyme (Table 2). Another oral *IDH2* mutant inhibitor, Enasidenib, is reported to enhance molecular remissions and mitigate hematopoietic differentiation damage in patients with AML (Table 2) [48]. *IDH* mutations are also present in chondrosarcoma. Li *et al.* [49] indicated that another dose-dependent *IDH1* mutant inhibitor, AGI-5198, decreased the level of D-2HG, downregulated colony formation and

metastasis, derailed cell cycle regulation, and activated apoptosis (Table 2). In short, the therapeutic effects of novel mutant *IDH* inhibitors are very useful for cancer patients displaying mutations in *IDH*.

2.12 | PPP

The PPP physiologically regulates redox homeostasis via G6PD that transforms glucose-6-phosphate and contributes to ribose-5-phosphate and NADPH production (Figure 3) [50]. Though PPP is related to the Warburg effect, its precise role in cancer metabolism remains unclear. Li *et al.* [51] reported that transketolase (TKT), which is a part of a branch of the PPP that is known to sustain HCC progression, modulates ribose 5-phosphate (R5P) expression and nucleotide synthesis (Table 1 and Figure 2E). Du *et al.* [52] found that the p53 family member TAp73 activates the expression of the G6PD and triggers the biosynthesis of NADPH and ribose with attenuated ROS in osteosarcoma (Table 1 and Figure 3). Importantly, the PPP also plays a critical role in the regional spread and distant metastasis of cancers. McDonald *et al.* [53] revealed that the oxidative branch of the PPP propelled regional migration, while its suppression partly alleviated chromatin rewiring, oncogenic gene activity, and tumorigenesis in pancreatic ductal adenocarcinoma (PDAC). This indicates that an increase in PPP flux promotes tumor proliferation via a metabolic-epigenetic signaling pathway. Clinical analysis indicates that PPP blockade can be recognized as a reliable anti-tumor tool and the G6PD inhibitor polydatin functions as a novel anti-PPP agent of cancers, such as tongue cancer [54] (Table 2).

3 | LIPID METABOLISM

3.1 | Oncogenic effect

Lipid metabolism is a critical event in the survival of malignancies [55–57]. Serol regulatory element-binding protein (SREBP) has been historically recognized as a crucial element in lipid metabolism [58]. Liu *et al.* [59] proposed that SREBP activated high-level de novo lipogenesis in HCC via protein arginine methyltransferase 5 (PRMT5)-mediated methylation, which prevented ubiquitin-proteasome-mediated degradation of SREBP (Table 1). Xu *et al.* [60] reported that activated PCK1 prevented INSIG1/2 from complexing with intracellular lipid and triggered SREBP signaling related to lipogenesis in HCC, suggesting that SREBP has a central role in lipid metabolism (Table 1). However, in lung adenocarcinoma, hepatic metabolism is reprogrammed through an altered

pro-inflammatory response via signal transducers and activators of transcription 3-suppressor of cytokine signaling 3 (STAT3-Socs3) signaling, with the disruption of AKT, AMPK, and SREBP signaling, altered lipid metabolism is noted in these cells [61]. Active tumors present hyperactivation of lipid metabolism and reprogramming of physiological metabolic processes in distant organs.

Huang *et al.* [62] found that in HCC cells under nutrient stress, mitochondrial ketolytic promoter 3-oxoacid CoA-transferase 1 (OXCT1) was activated by serum starvation-stimulated mTOR complex 2 (mTORC2)-AKT axis, and drove ketone metabolism to the TCA cycle, while also inactivating AMPK. This observation suggests that HCC cells with poor nutrition status may rely on ketone bodies to support survival (Table 1 and Figure 2F). Human primary melanoma and hairy cell leukemia cells also show metabolic ketogenesis. Kang *et al.* [63] found that 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL) was activated by BRAF V600E-expressing melanoma and leukemia cells, resulting in the activation of the MEK-ERK pathway, the production of acetoacetate (Table 1). Ketolysis and ketogenesis are important for cancer cell activities, and targeting ketone body metabolism can be a novel strategy to develop drug candidates against malignancies.

3.2 | Anti-cancer effect

There is abundant evidence showing that fatty acids possess anti-cancer properties. In previous studies, T-cells pretreated with fatty acids were injected into patients to identify changes in functional T-cells [64]. It has been revealed that fatty acids may be used by CD8⁺ T-cells as energy sources. Thus, anti-tumor effects were observed when cells were simultaneously subjected to hypoxic and hypoglycemic environments [65]. Zhang *et al.* [66] also found that CD8⁺ tumor-infiltrating T-lymphocytes (TILs) improved peroxisome proliferator-activated receptor (PPAR)-alpha signaling and degradation of fatty acids under hypoglycemia and hypoxia. Further enhancing fatty acid catabolism sustains the effector function of T-cells, and improves antitumor efficacy.

Fatty acid metabolism is of great therapeutic interest in cancer patient populations. Omega-3 polyunsaturated fatty acids in the diet can partially inhibit CRC development [67]. Zhang *et al.* [68] discovered that epoxydocosapentaenoic acids (EDPs) derived from omega-3 fatty acids could block angiogenesis as well as endothelial cell migration and VEGF receptor 2-induced protease generation (Table 2). Omega-3 fatty acids may also be involved in certain anti-cancer metabolism pathways and exhibit potential preventive and inhibitory effects in cancer.

4 | PROTEIN MODIFICATION

4.1 | Dephosphorylation

Serine/threonine-protein phosphatase-mediated dephosphorylation is a key process in physiological conditions, though mutations in phosphatases are found to sustain malignant progression [69, 70]. Mei *et al.* [71] reported that the replication timing regulatory factor 1 (RIF1) triggered protein phosphatase 1 (PP1) to dephosphorylate axis inhibition protein (AXIN), and stimulated the Wnt/ β -catenin axis to support the proliferative invasion of NSCLC cells (Table 1 and Figure 5C). Another phosphatase, protein phosphatase 2A (PP2A), modulates most of the protein dephosphorylation events in the cell by distinct regulatory subunits. Alterations in the subunits disturbed PP2A function and induce oncogenic signaling [72]. Tang *et al.* [73] found that a PP2A regulatory subunit, STRN3, recruited and dephosphorylated MST1/2, which helps trigger the YAP signaling and suppress the Hippo tumor suppressor of gastric cancer (Table 1). Recently, Liu *et al.* [74] identified that PP2A inhibitors synergize with chemotherapeutic agents to suppress aberrant signal transduction in cancer. Targeting aberrant protein phosphatase represents a promising therapeutic strategy in cancer treatment.

4.2 | Ubiquitination

E3 ubiquitin ligase-induced ubiquitination significantly modulates protein posttranslational modifications in tumor maintenance [75]. Tang *et al.* [76] found that tripartite motif-containing 11 (TRIM11) sustained tumor-promoting estrogen receptor α (ER α) ubiquitination to further stabilize this receptor in metastatic breast carcinoma (Table 1). Liu *et al.* [77] demonstrated that in an inflammatory microenvironment, upregulation of Cullin-RING E3 Ligases (CRLs) and activation of c-Myc induced ST7 ubiquitination in colitis-associated cancer (CAC) (Table 1). Blocking the E3 ubiquitin-ligase may be a reasonable anti-tumor strategy in the clinic. Remarkably, Hakin-1, which functions as a specific inhibitor of the E3 ubiquitin-ligase Hakai, was found to inhibit the ubiquitination of E-cadherin and suppress EMT (Table 2), implying a potential strategy to restrict CRC [78]. The ubiquitination of some pivotal molecules by E3 ubiquitin-ligase modulates the activity of oncogenic signaling, and this feature may be potentially explored for designing molecularly targeted drugs for cancer treatment.

5 | AMINO ACID METABOLISM

5.1 | Glutamine metabolism

High levels of glutamine (Gln) in the blood provide a readily available source of carbon and nitrogen to support cancer cell activities. Wang *et al.* [79] reported that mitochondrial sirtuin5 (SIRT5) activated glutamate dehydrogenase 1 (GLUD1) and consequently facilitated the incorporation of Gln into the TCA cycle. This indicates the critical role of Gln metabolic rewiring in the malignant phenotypes of CRC (Table 1 and Figure 1C). Similarly, colon cancer-derived mitochondrial glutamic pyruvate transaminase 2 (GPT2)-regulated Gln catabolism is involved in the Warburg effect, which takes advantage of the fact that Gln is the dominant carbon source Gln for the TCA cycle (Figure 3 and Table 1) [80].

The oncogenic transcription factor c-MYC is regulated by the Menin gene, and drives cancer cell proliferation and metabolism *in vitro* and *in vivo* [81]. In kidney cancer, prostate cancer, and Burkitt lymphoma, c-MYC also triggers the upregulation of glutaminolysis to fuel tumor growth by increasing P5C synthase and P5C reductase 1-mediated proline biosynthesis from Gln; suggesting a metabolic link between Gln and proline (Table 1 and Figure 3) [82].

Alteration of Gln metabolism contributes to nucleotide biosynthesis and attenuates DNA damage. This leads to an increase in conventional radiotherapy resistance [83]. Targeting Gln metabolic pathways, such as glutaminolysis, may provide a therapeutic strategy to kill tumor cells. The oral glutaminase inhibitor CB-839 was reported to suppress Gln-derived metabolite production during tumor development [84, 85]. Cohen *et al.* [86] found that cetuximab (which targets EGFR) in combination with CB-839 improved therapeutic efficacy in cetuximab-resistant CRC (Table 2 and Figure 1D). Gregory *et al.* [87] reported that combining CB-839 with arsenic trioxide or homoharringtonine decreased Gln synthesis in hematologic malignancies, upregulated ROS in the mitochondria, and triggered tumor cell death (Table 2). Dual targeting of oncogenic signaling by combining CB-839 with another anti-tumor agent may be a potential strategy for reversing conventional resistance to therapy.

5.2 | Serine metabolism

Compared to normal tissue, cancer cells exhibit altered metabolism with the overexpression of serine synthesis pathway enzymes, such as phosphoglycerate dehydro-

genase (PHGDH), which converts 3-phosphoglycerate derived from glucose-6-phosphate into serine [88] (Figure 3). Sullivan *et al.* [89] found that the overexpression of PHGDH improved serine levels and sustained purine and nucleotide biosynthesis, which supported melanoma and breast cancer growth under serine deprivation (Table 1 and Figure 4D). Activation of serine synthesis resulted in the conversion of glucose to pyruvate via serine dehydratase (SDH), and rewired glycolysis in a pyruvate kinase-independent manner in pancreatic cancer cells [90] (Table 1 and Figure 3). Pacold *et al.* [91] reported that PHGDH suppression inhibited the production of nucleotides which derived from one-carbon units from glycolytic serine, even in the presence of exogenous serine, demonstrating that serine was a vital source of one-carbon for purine as well as deoxythymidine synthesis in breast cancer (Table 1). Thus, PHGDH might be a novel metabolic vulnerability, and the preclinical evaluation of PHGDH inhibitor could contribute to further therapeutic applications [92].

5.3 | Methionine metabolism

For mammalian cells, methionine metabolism is essential for epigenetic reprogramming and cell growth [93]. The methionine cycle flux also impacts the epigenetic state of tumor cells. Metabolomic studies indicated that in NSCLC stem cells, methionine cycle activity is dysregulated, and methionine consumption exceeded methionine regeneration. [94]. Proteomic and genomic analyses showed that methyltransferase nicotinamide N-methyltransferase (NNMT) expression contributed to the cancer-associated fibroblast (CAF) phenotype and caused depletion of S-adenosyl methionine, which is critical for ovarian cancer metastasis [95] (Table 1). Methionine-related interventions are potentially used to treat diseases of metabolic origin. Gao *et al.* [96] revealed that methionine limitation induced clinical responses in pathological models of chemotherapy-tolerated RAS-driven CRC and soft-tissue sarcoma. Targeting methionine uptake can partly influence cancer metabolism, which ultimately regulates multiple aspects of therapeutic outcomes in cancer.

5.4 | Aspartate metabolism

Unlike other amino acids, aspartate is not readily available in the blood, so proliferating cells, such as tumor cells, produce aspartate by themselves. For example, TCA cycle-derived OOA mediates aspartate biosynthesis, which plays a pivotal role in cellular processes [97] (Figure 3). Surprisingly, mitochondrial respiration generates sufficient

electron acceptors for sustaining aspartate production [98]. However, aspartate has poor cell permeability, while the amino acid asparagine is available in tumors. Sullivan *et al.* [99] found that asparaginase 1 (ASNase1) allowed inter-conversion between asparagine and aspartate in 143B cells (human osteosarcoma cells *in vitro*), and subsequently provided sufficient endogenous aspartate, leading to a significant acceleration of tumor growth (Table 1 and Figure 3). These studies revealed that facilitating metabolic aspartate depletion could help to treat cancer.

5.5 | Tryptophan metabolism

Indoleamine 2,3-dioxygenase (IDO) in tumor cells can metabolize tryptophan (Trp) and trigger kynurenine (KYN) biosynthesis, which suppresses T-cell proliferative growth and promotes an immunosuppressive TME [100]. Notably, intratumoral metabolites instigate other tumor-associated cell populations to stimulate Trp catabolism and impair immune function. In multiple myeloma (MM), tumor cells release IL-32 and trigger TAMS to produce IDO. This further antagonizes CD4⁺ T-cell proliferative growth, which decreases antitumor bioactive substance secretion [101] (Table 1). IDO modulates the immunosuppressive function via depletion of Trp and the accumulation of KYN. Thus, a combination of IDO inhibitors including 1-methyl tryptophan (1-MT) and chemotherapeutic agents containing doxorubicin could be considered as a potential treatment option [102] (Table 2).

5.6 | Amino acid metabolism-arginine deprivation

Arginine accelerates tumorigenesis via the enzyme argininosuccinate synthetase 1 (ASS1) which catalyzes the synthesis of argininosuccinate from citrulline and aspartate, and is the rate-limiting enzyme in arginine biosynthesis [103] (Figure 3). This enzyme can be targeted for developing arginine deprivation therapy in multiple tumor types. Huang *et al.* [104] identified that ASS1-deleted myxofibrosarcoma cells were sensitive to PEGylated arginine deiminase (ADI-PEG20) therapy, and ASS1 deletion was associated with unfavorable clinical results in patients. The feasibility of ADI-PEG20 targeted treatment therapy may be directly linked to the loss of ASS 1 (Table 2).

The availability of ADI-PEG20 is directly implicated in ASS deficiency in other cancer types. Kim *et al.* [105] pointed out that prostate cancer cells with mitigated ASS were susceptible to autophagy suppression and ADI-PEG20 therapy, while early autophagy was reported to

exert an initial protective effect for cancer cells. The above evidence suggests that ASS deletion, autophagy, and ADI-PEG20 efficiency could be interrelated (Table 2). ADI-PEG20 also induced autophagy-dependent death of breast cancer cells with the loss of ASS1, and attenuated de novo arginine synthesis derived from aspartate and citrulline, and arginine deprivation also caused mitochondrial damage and cytotoxic autophagy in cancer cells [106] (Table 2 and Figure 4E). Thus, robust arginine deprivation therapy merits exploration as a potential therapeutic strategy to treat cancer.

6 | OTHER METABOLIC PATHWAYS

6.1 | Bile acid metabolism

In most cases of sporadic CRC, intestinal bile acids (BAs) are risk factors linked to worse clinical outcomes. Fu *et al.* [107] showed that APC mutants could change the structure of BA, leading to the production of BAs such as tauro-beta-muricholic acid (T-betaMCA) and deoxycholic acid (DCA). This can lead to an impairment of intestinal farnesoid X receptor (FXR) function, resulting in DNA damage and adenoma-to-adenocarcinoma transformation in CRC (Figure 1E). BA metabolism alters the composition of the intestinal microbiome in the TME of CRC. Yachida *et al.* [108] observed increased BAs including deoxycholate in polypoid adenomas and/or intramucosal carcinomas, indicating a link between the human gut microbiome, BA metabolism, and the early stage of the development of CRC.

6.2 | Vitamin D metabolism

Epidemiological data have shown that vitamin D has anti-cancer function as it was associated with a decrease in CRC risk. Maalmi *et al.* [109] reported that CRC patients with plasma 25-hydroxyvitamin D (25-(OH)-D3) levels < 30 nmol/L had an extremely high mortality, and 25-(OH)-D3 deprivation led to a poor clinical prognosis. Song *et al.* [110, 111] analyzed a large number of samples and discovered that elevated blood 25-(OH)-D3 levels were associated with a decreased risk of CRC (Table 2). In addition to CRC, vitamin D boosts CD8⁺ T-cell function and decreases inflammation of the TME in breast cancer tissue (Table 2) [112]. Due to its anti-inflammatory and anti-tumor properties, vitamin D may be a promising candidate for use as an adjuvant in standard cancer immunotherapies.

6.3 | Trace element metabolism

Metabolic imbalances in trace elements are associated with multiple cancer-induced pathological conditions. For example, zinc homeostasis damage causes muscle wasting in cancer patients. Wang *et al.* [113] discovered that the activated zinc transporter ZRT- and IRT-like protein 14 (ZIP14) in metastatic cancer cells facilitated zinc uptake in muscle progenitor cells and inhibited MyoD and Mef2c, leading to mitigated muscle-cell differentiation. Another trace element, copper, enables cancer cell proliferation, especially in primary pancreatic cancer. Ishida *et al.* [114] highlighted that the tumor promoter copper interacts with cytochrome c oxidase and mediates oxidative phosphorylation and ATP production (Table 1). Trace elements in the TME may be capable of partially altering tumor metabolic phenotypes.

6.4 | Urea cycle metabolism

Arginine is the main source of urea. Arginine is cleaved to produce urea and ornithine. Ornithine supports citrulline biosynthesis in the mitochondria, and subsequently to arginine renewal, and this series of reactions is termed as the urea cycle (UC) [115] (Figure 3). UC dysregulation is a general metabolic feature of multiple cancer types. Lee *et al.* [116] reported the critical role of the UC disorder in nitrogen conversion toward the activation of carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase (CAD). This contributes to subsequent pyrimidine synthesis and a detectable hallmark constituted by transversion mutations at the nucleotides, nucleic acid and protein levels in prostate cancer, breast cancer, and lung carcinoma models (Figure 4F, Figure 3, and Table 1). The UC is a metabolic vulnerability in EGFR-driven NSCLC, and sustains cellular energetics upon inhibiting EGFR [117].

6.5 | Stress-mediated adrenaline metabolism

Stress mediates neurochemical and endocrinological alterations, and leads to increased levels of adrenaline in metastatic tumor initiation [118]. Chronic behavioral stress induces the sympathetic nervous system (SNS) and contributes to greater tumor burden and invasive growth in HCC and breast cancer. Huan *et al.* [119] identified that SNS supported HCC behaviors by targeting alpha1-adrenergic receptors (ARs) in Kupffer cells to modulate chronic liver inflammation, secretory interleukin-6 (IL-6) production, and transforming growth factor-beta

(TGF- β) production (Figure 2G). Cui *et al.* [120] demonstrated that stress-activated SNS stimulated the production of epinephrine which triggered LDHA to generate lactate and stabilize Myc, subsequently triggered SLUG and further sustained breast cancer stem-like properties (Figure 4G). Activated SLUG inactivates E-cadherin and accelerates breast cancer cell metastasis (Figure 4G) [121, 122]. Significantly, Daher *et al.* [123] identified that β -blockers enhanced CD8⁺ T-cell responses and propranolol could synergize with anti-cancer vaccines in cancer immunotherapies (Table 2). Thus, chronic stress-induced adrenaline signaling regulates metabolic rewiring in cancer progression, and this complements existing therapeutic strategies with beta-blockade.

6.6 | HMOX1-dependent pathway

In cancer development, the superinduction of oxidative stress response often causes depletion of tumor suppressors, with the concomitant accumulation of heme oxygenase 1 (HMOX1) and Bach1, a sensor and effector of heme [124]. HMOX1 contributes to create a microenvironment that promotes tumor initiation. In addition, HMOX1 and Nrf2 significantly correlate with specific organ colonization of malignancies [125]. Lignitto *et al.* [126] discovered that Nrf2 was presented in nearly 30% of lung cancer cases, and enabled metastasis by stimulating HMOX-1 activity which subsequently downregulated heme and suppressed Fbxo22 (a ubiquitin ligase)-induced degradation of Bach1 in NSCLC (Table 1 and Figure 5D). Potent HMOX-1 inhibitors may be effective in alleviating malignancies.

6.7 | Autophagy pathway

Autophagy predominates in cellular catabolic responses under nutrient or energy depletion [127], while tumor cell metabolism strikingly affects autophagic processes of the cell. Thomas *et al.* [128] found that genetic defects in mitochondrial complex I suppressed autophagy induced by mTOR inhibitors in cells with increased mitochondrial metabolism. However, the lack of the autophagy gene Atg5 in KRAS-driven cancer led to impaired asparagine metabolism, reduced mitochondrial function, and caused excessive mitochondrial fragmentation. This evidence supports the critical role of autophagy in KRAS-driven progression [129]. In addition, upon serum starvation or metabolic stress, the oncoprotein lysosomal protein transmembrane 4 beta (LAPTM4B) and the exocyst subcomplex Sec5 stimulated inactive EGFR to interact with the autophagy inhibitor Rubicon, resulting in a disassocia-

tion of the Beclin 1-Rubicon complex. Subsequently, initial autophagic activity was triggered, which correlated with tumorigenesis [130]. Autophagy may be positioned to tune tumor metabolism under poor nutritional conditions within the TME.

7 | METABOLOMIC PROFILING

Metabolic profiling helps in understanding the molecular mechanisms involved in individual tumors in cancers such as HCC. Tan *et al.* [131] provided serum profiling data and identified the diagnostic usefulness of taurocholic acid, lysophosphoethanolamine, and lysophosphatidylcholine, which indicate the aberrant metabolic properties in all HCCs. Metabolomics can help in the identification of underlying inflammatory metabolite markers for early HCC diagnosis. Aleksandrova *et al.* [132] conducted metabolic profiling in HCC, intrahepatic bile duct (IBD), gallbladder, and biliary tract cancers (GBTC), and identified the diagnostic role of C-reactive protein (CRP), IL-6, non-high-molecular-weight (HMW) adiponectin, and C-peptide, suggesting that inflammation and hyperinsulinemia are involved in hepatocarcinogenesis (Table 3).

Zhou *et al.* [133] performed serum metabolic profiling and reported that higher concentrations of arachidonic acid and lower levels of lysophosphatidylcholines (lysoPCs) with polyunsaturated fatty acid acyl chains, led to HCC development in conditions of chronic inflammation, and elevated serum endocannabinoids anandamide (AEA), and palmitoylethanolamide (PEA) could lead to HCC in hepatitis C virus (HCV)-positive patients (Table 3).

In addition, metabolomics method sheds light on the metabolic regulation of HCC after surgical resection. Ye *et al.* [134] proposed that post-surgical HCC patients displayed complex metabolic responses that promoted anabolic metabolism; they further identified 16 elevated metabolites in HCC recurrence as well as five feasible diagnostic markers including ethanolamine, lactic acid, phenylalanine, and ribose (Table 3).

Metabolomic profiling is diverse and flexible, and provides opportunities to also identify metabolic markers in other cancer types. Kozar *et al.* [135] utilized serum metabolomic profiling and identified ceramides and sphingomyelin compounds of specific chain lengths as diagnostic markers in epithelial ovarian cancer (Table 3). In addition, serum metabolomics indicated that N-oleoyl taurine correlated with impaired metabolism and contributed to prostate cancer pre-diagnosis [136] (Table 3). Additionally, metabolomics based on HNMR revealed that 2-hydroxyisobutyrate, 3-indoxylsulfate, and alanine from urine in gastric cancer and acetate from fecal metabolites

TABLE 3 Diagnostic metabolic biomarkers in cancer

Metabolic biomarker	Cancer type	Reference
Taurocholic acid, lysophosphoethanolamine and lysophosphatidylcholine	Hepatocarcinoma	Tan <i>et al.</i> , 2013 [131]
CRP, IL-6, non HMW adiponectin, and C-peptide		Aleksandrova <i>et al.</i> , 2014 [132]
AEA and PEA	Hepatocarcinoma infected with HCV	Zhou <i>et al.</i> , 2012[133]
Ethanolamine, lactic acid, phenylalanine, and ribose	Hepatocarcinoma after surgical resection.	Ye <i>et al.</i> , 2012 [134]
Chain lengths ceramides and sphingomyelins	Epithelial ovarian cancer	Kozar <i>et al.</i> , 2018 [135]
N-oleoyl taurine	Prostate cancer	Huang <i>et al.</i> , 2019 [136]
Acetate	Colorectal cancer	Lin <i>et al.</i> , 2019 [137]
2-hydroxyisobutyrate, 3-indoxylsulfate, and alanine	Gastric cancer	Chan <i>et al.</i> , 2016 [138]

Abbreviations: AEA, endocannabinoids anandamide; CRP, C-reactive protein; HCV, hepatitis C virus.; HMW, high-molecular-weight; IL-6, interleukin-6; NSE, neuron-specific enolase; PEA, palmitylethanolamide.

in patients with CRC exhibited higher diagnostic superiority than other metabolites in corresponding specimens (Table 3) [137, 138]. Metabolic signatures reflect the tumor tissue microenvironment, and metabolomics can enable the identification of sensitive diagnostic biomarkers for malignancies in a clinical setting.

8 | CONCLUSIONS AND OUTLOOK

In this review, we summarized a variety of sufficiently unrecognized metabolic signaling pathways in tumorigenesis, invasive metastasis, aggressive growth, and immunosuppressive reactions. Research on cancer metabolism has made great progress, and the genetic background and metabolic signatures of tumors, including the idiographic concepts mentioned above, are worth further exploration.

Cellular metabolism is a key link between the extracellular environment and intracellular processes, and cancer-specific metabolic rewiring frequently converts normal physiological metabolic processes, such as protein modification and diverse enzymatic reactions, into necessary protective barriers for proliferating tumors [139–141]. Tumor cell populations compete with the normal tissue for glucose, and rate-limiting stimulators subsequently coordinate the Warburg effect. In addition, increased anaerobic glycolysis provides sufficient building blocks of bioactive substances including purines and pyrimidines in combination with other equally crucial metabolites. In condition of glucose starvation, other metabolites are metabolized which not only provides energy supplies but also stimulates oncogenic alterations.

Therefore, identifying and further targeting the metabolic nodes of tumor cells is the promising therapeutic interventions in patients with malignancies.

Compared with most conventional diagnostic methods, metabolomics effectively analyzes accessible biofluid which contain abundant metabolic information therein in cancers. Some malignancies are lack of early diagnostic platform, and metabolomics contributes to search for circulating metabolic biomarkers and achieve clinical therapies such as early surgical resection of the cancer [142, 143]. New discoveries into cancer metabolic reprogramming provide metabolic vulnerabilities which promote cancer treatments. Increasing small molecule metabolic inhibitors loaded by nanomaterials are employed as adjuvants with conventional anti-tumor agents, which can improve biosafety of metabolic inhibitors. Furthermore, nanoplatform induces apoptosis of cancer cells by enhancing ROS production that suppresses tumor growth [144]. Nanoscale functional materials not only achieve anti-tumor functions of carried drugs but also improve cancer treatments.

In brief, tumor cells exhibit high metabolic activity and energy consumption, which causes exhaustion in cancer patients. Thus, it may be necessary to design therapeutic strategies to reduce the metabolic rate of tumor cells to decrease cancerous phenotypes caused by oncogenic mutations.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

Z.T. wrote the manuscript. Z.X. and J.Z. discussed and edited the manuscript. X.Z. and J.Z. designed the concept, edited the manuscript. X.Z. and J.Z. supervised the project. All authors agree on the final version.

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