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RESEARCH HIGHLIGHT

Uncovering the IL-1β-PCAF-NNT axis: A new player in ferroptosis and tumor immune evasion

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Chronic inflammation is recognized as a crucial hallmark of cancer. Interleukin-1β (IL-1β), one of the pro-inflammatory cytokines, plays an ambiguous or even contradictory role in cancer development [1]. While increased expression of IL-1β in the tumor microenvironment is associated with tumor development, and invasiveness [1], it has also shown anti-tumorigenic effects in other contexts [2]. Therefore, it is difficult to define IL-1β's role as either tumor-promoting or anti-tumorigenic in cancers. Further investigation of IL-1β in specific contexts is essential to comprehensively understand its role in cancers.

Protein acetylation is a prevalent post-translational modification in mammalian cells [3]. Many metabolic enzymes localized in mitochondria, which are involved in diverse metabolic pathways such as the tricarboxylic acid (TCA) cycle, the urea cycle, glycolysis, gluconeogenesis, glycogen metabolism, and fatty acid metabolism, have been identified to undergo acetylation, leading to changes in their protein stability and/or enzyme activity [4]. However, whether IL-1β plays a role in regulating the acetylation modification of mitochondria-localized metabolic enzymes remains poorly understood.

Nicotinamide nucleotide transhydrogenase (NNT) is a metabolic enzyme located on the inner mitochondrial membrane (IMM) that catalyzes the reduction of nicotinamide adenine dinucleotide phosphate ($NADP^+$) to NADPH at the expense of reduced nicotinamide adenine dinucleotide (NADH) and H^+ re-entry into the mitochondrial matrix. This leads to an increase in the mitochondrial NADPH/$NADP^+$ ratio [5]. Furthermore, NNT regulates redox homeostasis by preventing iron-sulfur (Fe-S) cluster oxidation in non-small cell lung cancer (NSCLC) cells [5]. A recent study by Han *et al.* [6] demonstrated that IL-1β stimulation induces acetylation and activation of NNT, resulting in elevated production of NADPH and maintenance of Fe-S clusters in mitochondria (Figure 1). This mechanism protects tumor cells from ferroptosis and immunotherapy.

The authors of this study aimed to investigate whether IL-1β regulates protein lysine acetylation in cancer cells. They discovered that while IL-1β stimulation had little impact on global protein acetylation, it did increase lysine acetylation on specific proteins in cancer cells

List of abbreviations: IL-1β, Interleukin-1β; TCA, tricarboxylic acid; NNT, Nicotinamide nucleotide transhydrogenase; IMM, inner mitochondrial membrane; $NADP^+$, nicotinamide adenine dinucleotide phosphate; NADPH, nicotinamide adenine dinucleotide phosphate; NADH, nicotinamide adenine dinucleotide; Fe-S, Iron-sulfur; NSCLC, non-small cell lung cancer; LC–MS/MS, Liquid chromatography separation and high-resolution mass spectrometry analysis; PCAF, p300/CBP-associated factor; GC, gastric cancer; PD-1, programmed cell death protein 1; IL-6, Interleukin-6; TNF-α, tumor necrosis factor alpha.

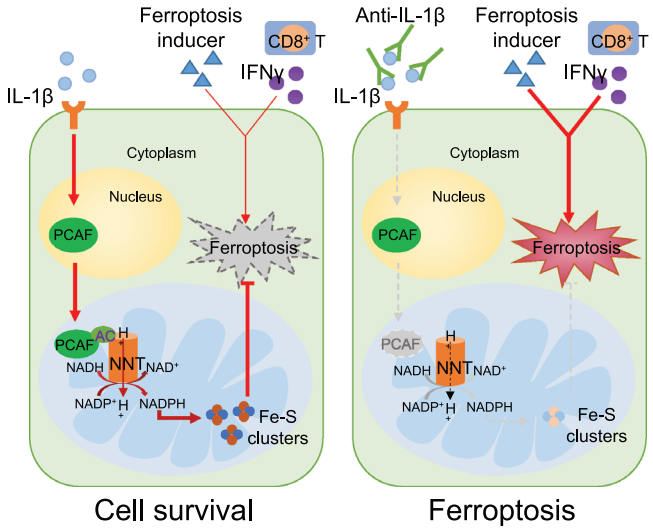

FIGURE 1 The IL-1β-PCAF-NNT axis regulates tumor cell ferroptosis and modulates tumor response to immunotherapy. Upon stimulation by IL-1β, the histone acetyltransferase PCAF translocates from the nucleus to the mitochondria, where it acetylates NNT at lysine residue 1042 (K1042ac). This acetylation enhances NNT's affinity for $NADP^+$ and leads to increased production of NADPH and maintenance of Fe-S clusters, ultimately protecting tumor cells from ferroptosis and conferring resistance to immunotherapy. This regulatory axis represents a potential therapeutic target for sensitizing tumors to immunotherapy by promoting ferroptosis.
Abbreviations: IL-1β: interleukin-1β; PCAF: p300/CBP-associated factor; AC: acetylation; NNT: nicotinamide nucleotide transhydrogenase; $NADP^+$: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate; NAD^+: nicotinamide adenine dinucleotide: reduced nicotinamide adenine dinucleotide; H^+: hydrogen ions; Fe-S: iron-sulfur cluster; $CD8^+$ T: cytotoxic T lymphocytes; IFN-γ: interferon-gamma; Anti-IL-1β: anti-IL-1β neutralizing antibody.

[6]. Using liquid chromatography separation and high-resolution mass spectrometry analysis (LC-MS/MS), they identified NNT as the protein that exhibited increased lysine acetylation in response to IL-1β stimulation [6]. Mechanistically, the authors found that upon IL-1β stimulation, histone acetyltransferase p300/CBP-associated factor (PCAF) translocates from the nucleus into mitochondria, where it acetylates NNT at K1042, facilitating NNT binding to $NADP^+$ and enhancing NNT enzyme activity. In vitro and in vivo experiments revealed that the IL-1β-PCAF-NNT axis increases NADPH production, sustaining Fe-S cluster maintenance in cancer cells, and thereby protecting tumor cells from ferroptosis and immunotherapy (Figure 1) [6]. The authors further validated their findings in clinical samples, demonstrating that NNT K1042 acetylation levels were positively correlated with the levels of extra-nuclear PCAF and IL-1β in gastric cancer (GC). Furthermore, higher levels of NNT K1042 acetylation correlated with more advanced disease stages and poorer overall survival in GC patients [6].

Ferroptosis is a form of regulated cell death caused by iron-dependent oxidative damage to membrane phospholipids [7]. The role of mitochondria in ferroptosis regulation is complex, as diverse metabolic activities in mitochondria drive ferroptosis, but mitochondria also possess factors that defend against it [8]. In this study, Han *et al.* [6] discovered that mitochondria-localized NNT can protect cancer cells against ferroptosis, thereby identifying another ferroptosis defense mechanism within mitochondria. This work enhances our basic understanding of mitochondria in ferroptosis regulation. Furthermore, Han *et al.* [6] demonstrated that targeting the IL-1β-PCAF-NNT axis in combination with programmed cell death protein 1 (PD-1) blockade significantly reduced tumor growth, at least partly by inducing tumoral ferroptosis, in multiple preclinical models.

Overall, the study by Han *et al.* [6] unveiled a novel role of the IL-1β-PCAF-NNT signaling axis in regulating ferroptosis and tumor immune evasion, highlighting its therapeutic potential in cancer therapy. However, several outstanding questions remain to be addressed in future studies. While the roles of other pro-inflammatory cytokines, such as Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), in ferroptosis regulation have been implicated in other contexts [9], their functions in regulating ferroptosis in tumor biology need further investigation. Moreover, while the present study mainly focuses on examining the involvement of the IL-1β-PCAF-NNT axis within cancer cells, its potential role in diverse immune cells necessitates further investigation; exploring this aspect will yield crucial insights into effectively targeting this signaling axis for cancer therapy. Likewise, given that IL-1β has a dual role in tumor biology and that PCAF has been shown to act as a tumor suppressor in GC through the PCAF-p16-CDK4 axis [10], the seemingly context-dependent role of the IL-1β-PCAF-NNT axis in tumor biology warrants careful preclinical studies to enable its therapeutic targeting in cancer. Furthermore, since a previous study demonstrated that depletion of NNT led to the accumulation of palmitoleic acid and oleic acid (both capable of influencing ferroptosis induction in cancer cells) [5], the involvement of NNT in lipid metabolism in the regulation of ferroptosis requires additional investigation. Finally, although the study focused on GC, given that IL-1β has been studied in various cancer types, it would be interesting to explore the generalizability of the findings to other cancer contexts.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Qidong Li drafted the manuscript. Boyi Gan provided critical revision of the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

Boyi Gan is an inventor on patent applications involving targeting ferroptosis in cancer therapy, and reports personal fees from Guidepoint Global, Cambridge Solutions, and NGM Bio. Qidong Li has no conflicts of interest to declare.

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