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.
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/CPB-associated factor (PCAF) translocates from the nucleus into 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/CPB-associated factor; AC: acetylation; NNT: nicotinamide nucleotide transhydrogenase; NADP⁺: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate; NAD⁺: nicotinamide adenine dinucleotide; Fe-S: iron-sulfur cluster; 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.
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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REFERENCES

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