RESEARCH HIGHLIGHT

Lysine metabolism at the nexus of crotonylation and tumor immunity

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A recent study by Yuan et al. in *Nature* explores the biological mechanisms underlying lysine catabolism and implicates histone crotonylation in antitumor immunity.

Cancer and cancer-associated immune cells alter metabolism to meet the demands of uncontrolled proliferation and altered effector function.[1–3] The metabolism of the amino acids such as methionine, serine, glutamine and the branched amino acids leucine, isoleucine, and valine, can regulate T cell activation and function, leading to the inhibition of tumor growth.[4–6] However, the pathological role of lysine in cancer has been less explored. A new study by Yuan et al. found a potential new role for lysine in antitumor immunity.[7]

Building on the previous observations in brain tumors, Yuan et al. found that lysine metabolism-related pathways were enriched in glioblastoma stem cells (GSCs). They observed elevated expression of lysine-dependent transport membrane protein solute carrier family 7 member 2 (SLC7A2) and increased activity of glutaryl-CoA dehydrogenase (GCDH) and lysine metabolism in glioblastoma (GBM) samples, as well as the upregulation of GCDH expression and the lysine metabolism pathway in GSCs. They further showed that the expression of crotonyl-CoA hydratase enoyl-CoA hydratase short chain 1 (ECHS1) was downregulated in GBMs and GSCs. This set of observations indicated that dysregulation of GCDH and ECHS1 in GSCs led to the accumulation of the intermediate metabolite crotonyl-CoA. Crotonyl-CoA is the precursor for histone lysine crotonylation (Kcr); the authors found that upregulation of GCDH and downregulation of ECHS1 in GSCs promoted histone H4 Kcr modification and tumor growth. Further, the author assessed the source of crotonyl-CoA in GSCs by testing the intracellular acyl-CoA levels after the knockdown of SLC7A2 or GCDH. They observed a significant reduction in crotonyl-CoA and a slight decrease in acetyl-CoA after disruption of lysine catabolism. L-lysine supplementation increased histone H4 Kcr and intracellular crotonyl-CoA levels, which was ablated by GCDH depletion. Accordingly, lysine catabolism was enhanced in GSCs, resulting in the production of crotonyl-CoA and the promotion of histone H4 Kcr modification. They further showed that type I interferon (IFN) signaling was induced by the disruption of lysine catabolism and suppressed GSC proliferation.

Notably, ~20% of GCDH was found in the nucleus of GSCs, raising the possibility of a regulatory mechanism mediated by nuclear-localized GCDH. They later revealed that reprogramming of lysine metabolism in GSCs influenced the expression of transposon elements (TEs) and showed that histone Kcr, derived from lysine catabolism, acted as a competitive epigenetic modification, regulating the chromatin environment and suppressing the formation of immunogenic TEs. Loss of histone Kcr promoted the production of immunogenic cytoplasmic double-stranded RNA (dsRNA) and dsDNA potentially through enhanced H3K27ac. This, in turn, stimulated the RNA sensor melanoma differentiation-associated protein 5 (MDA5) and the DNA sensor cyclic GMP–AMP synthase (cGAS), leading to enhanced type I IFN signaling, compromised tumorigenic potential, and increased $CD8^+$ T cell infiltration in glioma.

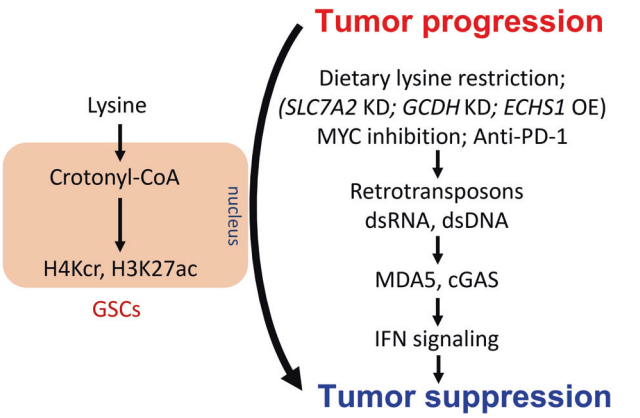

Fig. 1 Lysine catabolism reprograms tumor immunity through histone crotonylation. Graphical representation of the use of dietary lysine-restriction in conjunction with MYC inhibition or anti-PD-1 therapy. Kac lysine acetylation, KD knockdown, OE overexpression.

Finally, Yuan et al. explored the effects of a lysine-restricted diet. Their results indicated that consistent with the enhanced IFN signaling and functional $CD8^+$ T cell infiltration observed after GCDH loss, a lysine-restricted diet augmented the efficacy of MYC inhibition or anti-PD-1 therapy in restraining tumor growth and promoted $IFN\gamma^+CD8^+$ T cell infiltration (Fig. 1).

Overall, the study provides insights into lysine catabolism reprogramming and its impact on tumor immunity through histone crotonylation. These findings add a new dimension to the understanding of the mechanistic basis of dietary amino acid function in cancer therapy. However, it is crucial to consider several factors. Notably, although precision nutrition, such as dietary amino acids, can influence cancer metabolism, the extent

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to which changes in metabolic pathway activity result from nutrient uptake versus systemic organ-to-organ/cell-to-cell communication remains largely unknown. Analyzing these multiple effects will require considerable effort. Additionally, it is crucial to explore the potential competition between immune cells and cancer cells for amino acids, considering that immune cells have specific requirements for amino acids.[8] Nevertheless, this study provides another example of a link from metabolism to chromatin biology and demonstrates that dietary amino acid manipulations could affect the outcome of cancer.

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ADDITIONAL INFORMATION

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