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Methionine restriction and antitumor immunity

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Abstract

Recently, Fang *et al.* in *Cancer Cell* report that methionine restriction increases antitumor immunity by enhancing cyclic GMP-AMP synthase (cGAS) activity and promoting its dissociation from chromatin. This finding identifies a potential strategy to target cGAS demethylation in cancer therapy by altering methionine metabolism.

Keywords

methionine restriction; cGAS methylation; antitumor immunity

The metabolism of tumors as a target for cancer therapy has been a difficult topic to address. Understanding the regulatory mechanisms of the tumor immune microenvironment holds potential clinical value as it helps assess patient response to immunotherapy and identifies potential combinations with metabolic interventions. Dietary amino acids can reprogram the tumor microenvironment, which is a promising approach in cancer therapy [1–3]. However, our understanding of the impact of diet on cancer metabolism is in the very early stages. The cGAS-STING-type I interferon (IFN) signaling pathway is a crucial player in the innate immune response as well as tumor immunity [4–6]. Its activation has shown promise as an effective antitumor strategy when combined with immune checkpoint inhibitors [7–8]. cGAS is a major sensor for cytoplasmic double-stranded DNA (dsDNA) [4] and is also abundantly enriched in the nucleus [3], but the interaction between cGAS and chromatin is poorly understood. Likewise, it remains unclear whether the metabolism of amino acids affects cGAS-STING signaling and whether it can be effectively combined with ionizing radiation–another major therapy for consideration-along with immune checkpoint inhibitors. To address such questions Fang *et al.* assessed the regulation of cGAS-STING signaling by nutrient stress and highlighted the potential of targeting cGAS demethylation in cancer therapy [9].

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Declaration of interests

JWL advises Restoration Foodworks, Nanocare Technologies, and Cornerstone Pharmaceuticals.

Notably, they identified methylation sites at K362 (K350 in mice) that were responsive to methionine (Met) and S-adenosylmethionine (SAM) availability, suggesting that methionine plays a role in limiting activation of the cGAS-STING pathway by inhibiting cGAS activity. Further, they found that cGAS methylation requires the regulation of the methyltransferase SUV39H1, which can inhibit cGAS activity by blocking cGAS binding to DNA and dimerization. K362 methylation promotes nuclear aggregation and chromatin tethering of cGAS. UHRF1, ubiquitin-like with PHD and ring finger domains 1, a methylation recognition protein [10], recruits methylated cGAS to promote its binding to chromatin. The authors showed that short-term methionine restriction or targeted intervention of the SUV39H1-UHRF1 axis reduces cGAS methylation.

Fang *et al.* next investigated the pathological role of targeting the SUV39H1-cGAS-UHRF1 axis in tumor growth. The authors demonstrated that tumor cells and host methylation loss or a methylation mimic modification can inhibit endogenous cGAS activity and promote tumor immune escape. The combination of methionine restriction and the SUV39H1 inhibitor reshapes the tumor immune microenvironment, improves the efficacy of radiotherapy, and inhibits tumor growth. The authors further investigated the methylation of cGAS in colorectal cancer samples and found it to have a negative correlation with the prognosis of individuals.

In summary, Fang *et al.* revealed that methionine-SUV39H1-UHRF1 regulates cGAS chromatin tethering and activity through methylation, which provides an important potential targeted intervention strategy for activating the cGAS-STING pathway to promote anti-tumor immunity (Fig. 1). Many mechanisms remain to be fully understood, such as the long-term methionine deprivation that may cause complex consequences, and the high metabolic demand of cancer cells that results in their competition with immune cells for amino acid resources. Nevertheless, in view of cGAS in antiviral infection, autoimmune diseases, and tumor immunity, the inhibition of cGAS activity by methylation modification may be a key switch for immune response regulation, which is worthy of further exploration and adds a new dimension to understanding nutrient function in cancer therapy.

Acknowledgments

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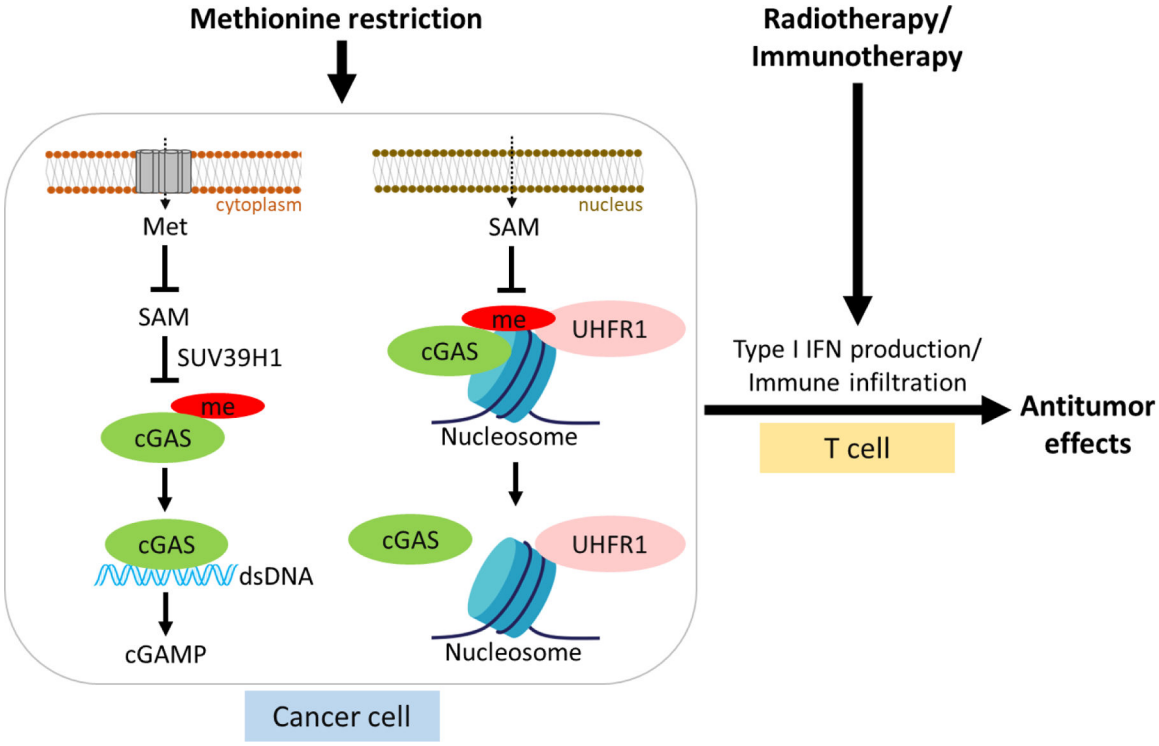

Figure 1.

Methionine-mediated methylation recruits UHRF1 to regulate cGAS methylation and its dissociation from chromatin and remodel the tumor immune microenvironment.