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Metabolic and functional adaptation of regulatory T cells in the tumor microenvironment

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Abstract

Regulatory T cells (Treg cells) are essential for immune tolerance, but also drive immunosuppression in the tumor microenvironment. Therapeutic targeting of Treg cells in cancer will therefore require the identification of context-specific mechanisms that affect their function. Here we show that inhibiting lipid synthesis and metabolic signaling that are dependent on sterol-regulatory-element-binding proteins (SREBPs) in Treg cells unleashes effective antitumor immune responses without autoimmune toxicity. We find that the activity of SREBPs is upregulated in intertumoral Treg cells. Moreover, deletion of SREBP-cleavage-activating protein (SCAP)—a factor required for SREBP activity—in these cells inhibits tumor growth and boosts immunotherapy that is triggered by targeting the immune-checkpoint protein PD-1. These effects of SCAP deletion are associated with uncontrolled production of interferon-γ and impaired function of intertumoral Treg cells. Mechanistically, signaling through SCAP and SREBPs coordinates cellular programs for lipid synthesis and inhibitory receptor signaling in these cells. First, de novo fatty-acid synthesis mediated by fatty-acid synthase (FASN) contributes to functional maturation of Treg cells, and loss of FASN from Treg cells inhibits tumor growth. Second, Treg cells in tumors show enhanced expression of the PD-1 gene, through a process that depends on SREBP activity and signals via mevalonate metabolism to protein geranylgeranylation. Blocking PD-1 or SREBP signaling results in dysregulated activation of phosphatidylinositol-3-kinase in intertumoral Treg cells. Our findings show that metabolic reprogramming enforces the functional specialization of Treg cells in tumors, pointing to new ways of targeting these cells for cancer therapy.