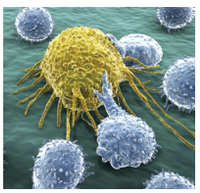
Metabolism

Major finding: Tumor cell–induced glucose deprivation inhibits T-cell glycolysis and immunogenic functions *in vivo*.

Mechanism: Loss of PEP-mediated SERCA regulation under glucose-restricted conditions inhibits Ca^{2+}-NFAT activation.

Impact: Immune checkpoint inhibitors promote tumor suppression by reestablishing glycolysis in T cells.

TUMOR GLUCOSE CONSUMPTION INHIBITS T-CELL FUNCTION



T-cell dysfunction is thought to contribute to immune system evasion by tumor cells and can be caused by multiple environmental factors. For example, *in vitro* experiments suggest that proper T-cell function is dependent on glucose, which can be in low supply within the tumor microenvironment. Using a mouse sarcoma model, Chang, Qiu, and colleagues showed T cells produced significantly less IFNγ when cultured with tumor cells than when cultured alone, but that the addition of glucose could restore IFNγ production, suggesting that competition with tumor cells for glucose suppresses T-cell activation. Compared with an antigenic sarcoma clone that regresses *in vivo*, progressor sarcomas displayed increased glycolytic activity, and tumor-infiltrating lymphocytes (TIL) isolated from progressor tumors were hyporesponsive and showed reduced glycolysis and increased markers of nutrient deprivation, demonstrating that tumor cells suppress T-cell function by limiting glucose availability in the extracellular milieu. Consistent with this possibility, increasing regressor tumor cell glycolysis by increasing glucose exposure or overexpressing MYC was sufficient to reverse regression and promote tumor growth. Immune checkpoint blockade therapy enhanced glycolytic activity and cytokine production in TILs by directly inhibiting AKT/mTOR-driven glycolysis in tumor cells, providing evidence for a function of immune checkpoint inhibitors beyond direct regulation of T-cell signaling. Ho and colleagues similarly observed that glucose limitation in the tumor microenvironment and increased tumor glycolysis dampen TIL activation, and showed that low T-cell levels of phosphoenolpyruvate (PEP), a glycolytic metabolite that inhibits the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), reduces Ca^{2+} and NFAT1 signaling and thus suppresses antitumor responses. Metabolic rewiring of T cells by overexpressing phosphoenolpyruvate carboxykinase 1 increased PEP production and T-cell effector function and suppressed tumor growth. Together, these studies illustrate how tumor cell–induced metabolic reprogramming of T cells suppresses their activation and provide further insight into the mechanism of action of immune checkpoint inhibitors and potential strategies to boost antitumor immunity. ■

Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell 2015;162:1229–41.

Ho PC, Bihuniak JD, Macintyre AN, Staron M, Liu X, Amezquita R, et al. Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. Cell 2015;162:1217–28.

Leukemia

Major finding: *Ikzf1* alterations induce stem cell–like properties in BCR–ABL1$^+$ ALL that are abrogated by retinoids.

Mechanism: Retinoids inhibit adhesion and self-renewal in part by inducing wild-type IKZF1 expression.

Impact: Retinoids improve the therapeutic response to dasatinib in BCR–ABL1$^+$ ALL harboring *IKZF1* alterations.

RETINOIDS SENSITIZE *IKZF1*-MUTANT BCR–ABL1$^+$ ALL CELLS TO DASATINIB

Acute lymphoblastic leukemia (ALL) results from the overproliferation of immature lymphoid cells that fail to differentiate into mature lymphocytes. Deletions or mutations in *IKZF1*, which encodes the lymphoid transcription factor IKAROS, are a hallmark of BCR–ABL1$^+$ ALL, but the effects of these alterations on disease progression and therapeutic response are not well understood. Churchman and colleagues found that expression of the dominant-negative IK6 isoform of IKZF1 (in which the DNA-binding zinc fingers are deleted) and deletion of *Arf* cooperated to drive formation of B-progenitor lymphoid ALL in a mouse transplant model of BCR–ABL1$^+$ leukemia. In addition, expression of IK6 or *Ikzf1* haploinsufficiency reduced the therapeutic response of BCR–ABL1$^+$ ALL to the tyrosine kinase inhibitor (TKI) dasatinib. Analysis of the transcriptome and proteome of *Ikzf1*-altered *Arf*$^{-/-}$;BCR–ABL1$^+$ pre-B cells revealed overexpression of multiple adhesion molecules that are transcriptionally repressed by IKZF1, consistent with the increased bone marrow stromal adherence of *Ikzf1*-altered cells. Furthermore, *Ikzf1* alterations resulted in the enrichment of stem cell–related genes and enhanced self-renewal *in vitro*. Given the association between stem cell–like and adhesive properties with poor response to TKIs, the authors performed a high-throughput screen to identify TKI-sensitizing agents that abolish the self-renewal capacity of IK6-expressing *Arf*$^{-/-}$; BCR–ABL1$^+$ ALL cells. Addition of retinoid compounds targeting different retinoid receptors arrested cell proliferation without direct cytotoxicity and abrogated the stem cell–like phenotype of *Ikzf1*-altered pre-B cells. This effect resulted, in part, from retinoid-mediated induction of wild-type IKZF1, but not IK6, in BCR–ABL1$^+$ leukemia cells. Moreover, coadministration of dasatinib with the synthetic retinoid bexarotene increased the response to dasatinib and prolonged the survival of mice bearing *IKZF1*-altered leukemia. These results characterize the role of *IKZF1* alterations in high-risk ALL and highlight a potential therapeutic strategy to improve therapeutic responses in patients with BCR–ABL1$^+$ ALL. ■

Churchman ML, Low J, Qu C, Paietta EM, Kasper LH, Chang Y, et al. Efficacy of retinoids in IKZF1-mutated BCR-ABL1 acute lymphoblastic leukemia. Cancer Cell 2015;28:343–56.