RESEARCH WATCH

Myeloproliferative Disease

Major finding: *Ptpn11* activating mutations in bone marrow MSPCs and osteoprogenitors induce MPN in mice.

Approach: Lentiviral transduction into bone marrow of *Ptpn11* mutant mice enhanced the production of CCL3, which recruits monocytes to the site of disease.

Impact: CCL3 is a potential target for inhibiting Noonan syndrome-associated leukemogenesis.

PTPN11 MUTATIONS IN THE BONE MARROW MICROENVIRONMENT INDUCE LEUKEMIA

Myeloproliferative neoplasms (MPN) are blood disorders which arise from the overproduction of myeloid cells by the bone marrow (BM). Mutations in the protein tyrosine phosphatase SHP2 (encoded by *PTPN11*) occur in approximately half of patients with Noonan syndrome, who have an increased risk of developing leukemias, including the childhood MPN juvenile myelomonocytic leukemia (JMML). To elucidate the role of *Ptpn11* mutations in the murine BM microenvironment, Dong, Yu, Zheng, and colleagues interrogated a genetically engineered mouse model of *Ptpn11* mutation–driven MPN which they had previously generated. *Ptpn11* E76K/Nestin-Cre+ mice, in which BM mesenchymal stem/progenitor cells (MSPC)—which are Nestin+—but not MPN cells expressed mutant *Ptpn11*, developed profound MPN. Further expression of *Ptpn11* E76K in both murine hematopoietic cells and BM stromal cells resulted in MPNs that were more severe and progressive than MPNs induced by the expression of *Ptpn11* E76K in murine hematopoietic cells. Cell type–specific expression of *Ptpn11* E76K identified MSPCs and osteoprogenitor cells as the BM cell types that induced MPN development. *Ptpn11* E76K MSPCs and MPN cells were shown to overproduce, respectively, the C-C motif chemokine 3 (CCL3) and IL1β, both of which were also highly produced by *PTPN11* mutant human MSPC and JMMML cells. *Ptpn11* E76K MSPC–derived CCL3 recruited monocytes to the area where MSPCs and hematopoietic stem cells (HSC) reside, and these monocytes released IL1β to hyperactivate HSCs and induce MPN. Consistent with these findings, treatment of MSPC-specific *Ptpn11* E76K mice with CCL3 receptor antagonists reversed MPN-associated phenotypes. Together, these findings demonstrate how *Ptpn11* mutations in the BM microenvironment drive MPN development and suggest that inhibiting CCL3 may prevent leukemic progression of MPN and improve stem cell transplantation therapy in patients with Noonan syndrome.


L-ARGININE REGULATES T-CELL METABOLISM TO PROMOTE ANTITUMOR ACTIVITY

T-cell survival and antitumor activity are dependent on metabolic fitness, and activated T cells adapt their metabolism to use large amounts of glucose, amino acids, and fatty acids. To characterize metabolic adaptations underlying T-cell activation, Geiger and colleagues used high-resolution mass spectrometry to analyze the proteome and metabolome of activated T cells. A total of 2,824 differentially expressed proteins were identified in activated T cells compared with nonactivated T cells, and upregulated proteins included enzymes involved in several metabolic pathways including arginine metabolism. Of 429 identified metabolites, 49 were increased upon T-cell activation and only 14 were decreased, including three members of the same metabolic pathway: arginine, ornithine, and N-acetylornithine. T-cell activation resulted in a rapid decrease in intracellular arginine despite enhanced L-arginine uptake due to the rapid conversion of L-arginine into downstream metabolites, mainly by the mitochondrial enzyme arginase 2 (ARG2), which was upregulated in activated T cells. T cells activated in L-arginine–supplemented medium consumed less glucose and exhibited reduced expression of glucose transporters and glycolytic enzymes, altogether indicating that L-arginine reduced glycolytic flux. Conversely, oxidative phosphorylation was enhanced by increased intracellular L-arginine in activated T cells. In addition to the metabolic affects, L-arginine influenced the fate of activated T cells; elevated L-arginine levels limited T-cell differentiation and promoted the maintenance of central-memory T-cell characteristics. Further, L-arginine increased the survival of activated CD4+ and CD8+ T cells. In vivo, supplementation with L-arginine enhanced activated T-cell survival, and adoptive transfer of L-arginine–treated cells activated by tumor antigen resulted in an enhanced antitumor response in melanoma xenografts. Together, these findings indicate that L-arginine promotes T-cell survival and antitumor activity and suggest that L-arginine may have the potential to enhance T-cell therapies.


**Metabolism**

Major finding: L-arginine controls T-cell metabolism and promotes T-cell survival to enhance antitumor immunity.

Approach: High-resolution mass spectrometry characterized the proteome and metabolome of activated T cells.

Impact: L-arginine enhances antitumor T-cell responses and may potentially improve T-cell therapies.
L-Arginine Regulates T-cell Metabolism to Promote Antitumor Activity


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