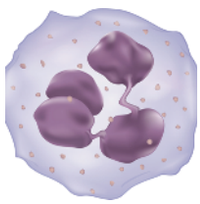
Tumor Microenvironment

Major finding: MET is critical for antitumor neutrophil infiltration to HGF-secreting tumors and inflammatory sites.

Mechanism: MET induction by inflammatory stimuli enables neutrophil transendothelial migration and cytotoxicity.

Impact: Targeted MET inhibition in cancer cells may enhance efficacy without dampening neutrophil responses.

MET PROMOTES ANTITUMOR NEUTROPHIL RECRUITMENT AND CYTOTOXICITY



Amplification or mutation of the proto-oncogene *MET* is required for the growth and survival of many tumors, making it a promising therapeutic target. However, MET expression and function in tumor-associated stromal cells is not well characterized. Finisguerra and colleagues found that deletion of *Met* in the hematopoietic compartment or specifically in neutrophils resulted in enhanced growth and metastasis of various hepatocyte growth factor (HGF)–secreting tumors, including lung and hepatocellular carcinomas, melanomas, fibrosarcomas, and mammary and colorectal cancers. *Met* deficiency resulted in reduced numbers of tumor-associated neutrophils (TAN) in primary tumors and metastases, whereas reconstitution of MET expression in neutrophils increased their recruitment and blocked tumor growth, supporting the idea that MET is critical for antitumor neutrophil infiltration into tumors. Specific knockdown of MET in cancer cells more effectively suppressed tumor growth compared with systemic administration of MET inhibitors, revealing that MET blockade in antitumor neutrophils limits the therapeutic efficacy of systemic MET inhibition. The expression of MET in neutrophils was enhanced in tumor-bearing mice and human non–small cell lung tumors compared with healthy tissue and was induced by inflammatory stimuli such as TNFα. Systemic inactivation of TNFα inhibited MET expression in TANs and prevented TAN accumulation in tumors by blocking neutrophil chemotaxis toward HGF and transendothelial migration of neutrophils to inflammatory sites. Furthermore, *Met* deletion in neutrophils reduced the expression of inducible nitric oxide synthase, a marker of antitumor neutrophils, and impaired nitric oxide production, resulting in decreased cancer cell killing capacity. Together, these data demonstrate that, whereas MET promotes cancer cell proliferation and survival, it enhances the recruitment and cytotoxic function of antitumor neutrophils, suggesting that MET inhibition specifically in cancer cells may improve the efficacy of MET-targeted therapies. ■

Finisguerra V, Di Conza G, Di Matteo M, Serneels J, Costa S, Thompson AA, et al. MET is required for the recruitment of anti-tumoural neutrophils. Nature 2015 May 18 [Epub ahead of print].

Immunotherapy

Major finding: Adoptive transfer of activated marrow-infiltrating lymphocytes (MIL) induces anti-myeloma immunity.

Concept: MILs exhibit enhanced polyclonal tumor specificity and increased persistence in the bone marrow.

Impact: The use of MILs may improve adoptive T-cell therapy in patients with hematologic malignancies.

MARROW-INFILTRATING LYMPHOCYTES ARE EFFECTIVE IN MULTIPLE MYELOMA

Adoptive T-cell therapy (ACT) using activated tumor-specific T cells has been proposed as a potential approach to stimulate antitumor immunity following myeloablative chemotherapy in patients with multiple myeloma (MM). However, the efficacy of ACT is limited by the ability to enrich for tumor-specific T cells. Preclinical studies have revealed that activated marrow-infiltrating lymphocytes (MIL) from the bone marrow tumor microenvironment exhibit polyclonal tumor specificity and effectively target MM plasma cells *in vitro*, suggesting that ACT using MILs may facilitate enrichment for myeloma-specific T cells and result in greater antitumor immunity. Noonan and colleagues performed a phase I study to assess the feasibility, safety, and efficacy of this approach in 25 patients with newly diagnosed or relapsed multiple myeloma. MILs were harvested from all patients, expanded and activated *ex vivo*, and infused following autologous peripheral stem cell transplant in 22 patients, resulting in complete remission (CR) in six patients, partial response in seven patients, and stable disease in five patients. In addition, a greater than 90% reduction in tumor burden was associated with prolonged progression-free survival (25.1 months versus 11.8 months). Analysis of immune responses within the bone marrow indicated that the likelihood of achieving a CR was associated with greater antimyeloma specificity of activated MILs *ex vivo*, the presence of a $CD8^+$ central memory T-cell phenotype and decreased IFNγ-producing effector T cells at baseline, and increased $CD8^+$ T-cell cytotoxic activity. Furthermore, MILs persisted over time in the bone marrow, resulting in sustained myeloma-specific immune responses at one year after ACT in patients who achieved a CR. These findings demonstrate that MILs represent a source of tumor-specific T cells for ACT and support ongoing clinical trials to further evaluate the efficacy of this approach in patients with hematologic malignancies. ■

Noonan KA, Huff CA, Davis J, Lemas MV, Fiorino S, Bitzan J, et al. Adoptive transfer of activated marrow-infiltrating lymphocytes induces measurable antitumor immunity in the bone marrow in multiple myeloma. Sci Transl Med 2015;7:288ra78.