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Targeting STAT3 in neutrophils alters their immunoregulatory activity in cancer

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Abstract

Myeloid cells are a major component of immune cells infiltrating tumors, interacting with each other, with tumor cells and other stromal cells, and demonstrating a prominent plasticity. Neutrophils, as a population of such cells, contribute to cancer progression via multiple mechanisms, including stimulation of angiogenesis and the regulation of adaptive immune responses. Importantly, neutrophils were demonstrated to be associated with poor clinical outcome in patients with different kinds of cancer, including head and neck cancer, renal cancer, non-small-cell lung carcinoma or melanoma. Enrichment of neutrophils was also associated with metastases in various tumor entities.

Activity of neutrophils strongly depends on the cytokines or growth factors present in the microenvironment. Since these cells are highly plastic and their functionality can be easily altered, they are ideal target for anti-tumor therapies. Since we observe that elevated STAT3 is associated with pro-tumoral activity of neutrophils, we tested here the approach to functionally reprogram these cells by the inhibition of STAT3 signaling pathway. We could show that such STAT3 inhibition solely in neutrophils led to decreased tumor growth and metastasis in cancer, which was accompanied by a significant expansion of $CD8^+$ cytotoxic T cells in tumors and tumor-draining lymph nodes (TDLNs). Comprehensive multiparameter analyses of tumors and TDLNs revealed a significant enrichment of $CD8^+$ T cell subsets with strongly cytotoxic activity, which effectively killed cancer cells *in vitro*. These findings provide novel insights in therapeutic avenues and suggest neutrophil-targeted STAT3 inhibition as a promising opportunity for cancer immunotherapy.