

PRIMER

Dismantling the tumoral cloak of self-protection

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Tumors protect themselves from immune clearance by promoting extramedullary hematopoiesis. A new study in PLOS Biology provides insights into the mechanisms underlying this process, which may hold the key to disrupting generation of the immunosuppressive tumor microenvironment.



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Abbreviations: EMH, extramedullary hematopoiesis; HSPC, hematopoietic stem and progenitor cell; LIF, leukemia inhibitory factor; MDSC, myeloid-derived suppressor cell.

Tumors have ingenious means of self-protection. They can lure hematopoietic stem and progenitor cells (HSPCs), the body's blood producing cells, away from their natural home in the bone marrow to new places, such as the spleen [1]. There, the HSPCs are instructed to make immunosuppressive myeloid cells that blunt antitumor immunity, thereby shielding the tumor in a cloak of self-protection.

The evidence for protective myelopoiesis in the setting of solid organ malignancies extends across multiple tumor types including breast, colon, and lung [2]. In patients with malignancies, a high neutrophil to lymphocyte ratio, a measure of the degree of myelopoiesis, portends a poor prognosis [3]. This is thought to be because production of myeloid cells, including myeloid-derived suppressor cells, inhibits cytotoxic immune responses by T cells and NK cells that are critical for antitumor immunity. Such immunosuppressive tumor microenvironments are a major obstacle in immunotherapeutic approaches to cancer. Thus, the mechanisms by which tumors raise this cloak of protection are the subject of intense interest.

In a new article in *PLOS Biology*, Barisas and colleagues report a rigorous study that sought to understand how tumors attract and support extramedullary hematopoiesis (EMH) in the spleen [4] (Fig 1). They identify two complementary mechanisms by which tumors draw HSPCs to the spleen to produce myeloid cells, including neutrophils. Using a heterotopic tumor transplantation model, the investigators examined mechanisms of neutrophilia in the setting of breast cancer. They found that tumors produced the inflammatory cytokine IL-1 α , which was found at increased levels in the circulation of tumor-bearing mice. Single-cell RNA-seq revealed a pro-inflammatory gene signature in HSPCs at extramedullary sites in tumor-bearing mice, including expression of TNF α and NF κ B, a common stress response regulator triggered by pro-inflammatory cytokines such as interferons and pathogen recognition receptors such as Toll-like receptors. Injection of IL-1 α into mice was sufficient to induce TNF α production by HSPCs, suggesting a mechanism of direct communication between tumors and HSPCs.

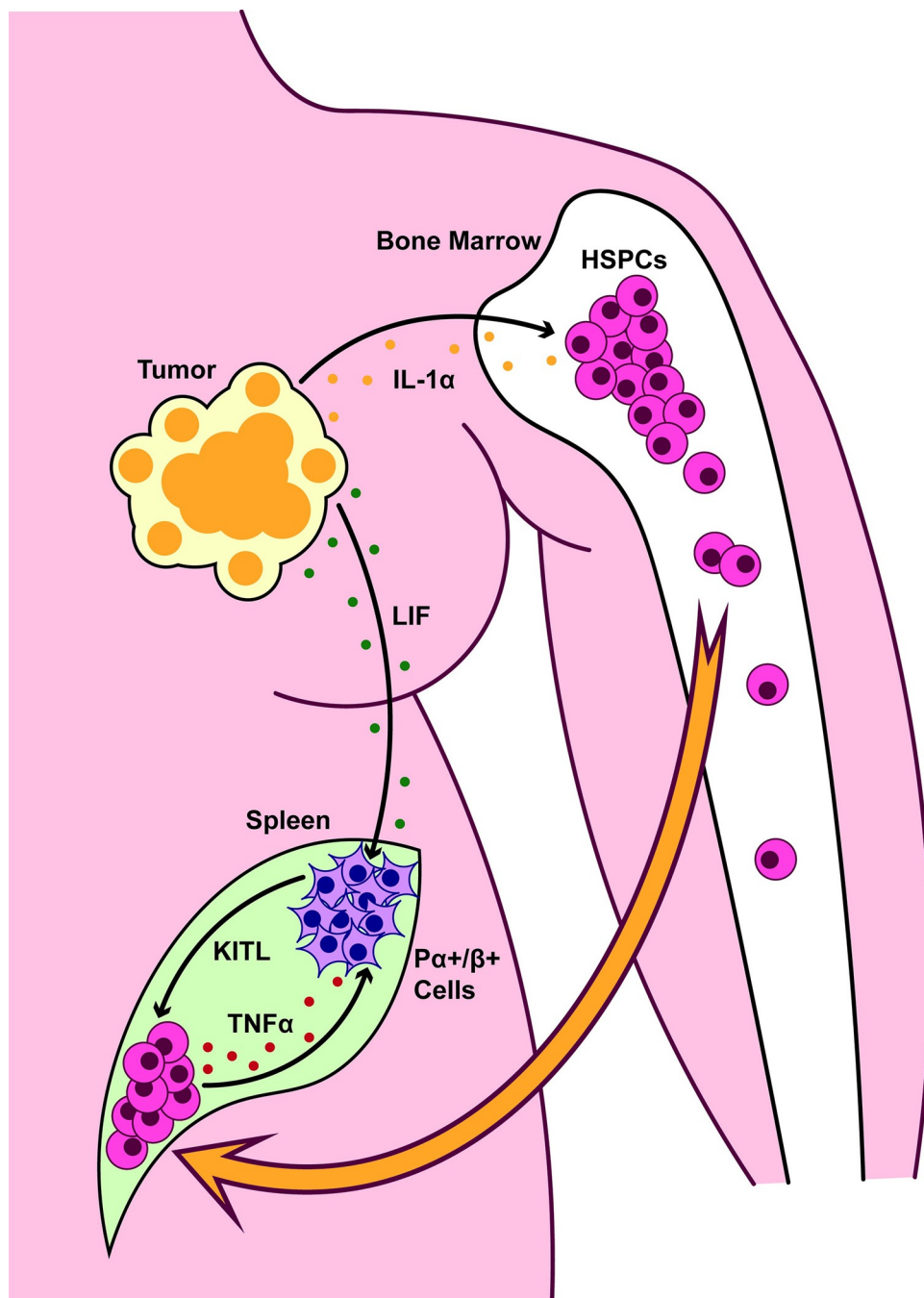


Fig 1. IL-1 α and LIF produced by tumors promotes extramedullary hematopoiesis by inducing HSCP-derived TNF α and activation of splenic ABS cells. Tumor cells produce IL-1 α , which activates TNF α expression by HSPCs. TNF α and tumor-derived LIF are sensed by splenic Pdgfra⁺/Pdgrfb⁺ stromal (ABS) cells, which produce cytokines such as CXCL12 and KITL (also known as SCF) to promote homing of HSPCs. Thus, tumor-derived factors promote splenic extramedullary hematopoiesis, a source of immunosuppressive myeloid cells that facilitate immune evasion. HSPC, hematopoietic stem and progenitor cell; LIF, leukemia inhibitory factor.

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Pro-inflammatory cytokines are known to have powerful effects on HSPCs, inducing their migration, division, and myeloid differentiation [5,6]. Indeed, a recent study showed that pro-inflammatory cytokines produced during murine sepsis were sufficient to induce myeloid

differentiation and, more specifically, production of myeloid-derived suppressor cells (MDSCs) [7]. Cytokine-dependent production of MDSCs by HSPCs may be a natural mechanism by which the body down-regulates inflammatory responses to an acute infectious challenge.

In the study by Barisas and colleagues, deletion of *IL1A* from the tumor cells decreased TNF α and total splenic myeloid progenitors [4]. A population of Pdgfra⁺/Pdgrfb⁺ stromal (ABS) cells in the spleen strongly express TNF α receptor and the HSPC growth cytokine KITL (also known as SCF). In vitro studies indicated that these cells respond to TNF α to attract and support the growth of bone marrow-derived HSPCs in the spleen. Notably, tumor-bearing mice receiving IL-1 receptor blocking antibody had decreased neutrophilia.

Next, the investigators also demonstrated production of leukemia inhibitory factor (LIF) by tumor cells, which induced expansion of HSPC and myeloid progenitors in the spleen and promoted neutrophilia. LIF is a cytokine that inhibits differentiation, thereby promoting expansion of undifferentiated cells. LIF receptor was required for ABS cells to support hematopoiesis, including by the production of stem cell homing and growth factors such as CXCL12 and SCF. Thus, the tumor-derived IL-1 and LIF cooperate to promote EMH in cancer. The authors have yet to demonstrate that the myeloid cells resulting from tumor-derived IL-1 and LIF truly function as MDSCs. Nevertheless, the combined release of these two cytokines by tumors may represent an example of tumors coopting a natural homeostatic response to generate self-protective antitumor responses. Importantly, tackling this mechanism may be an effective avenue to overcome the immunosuppressive microenvironment that continues to represent a major barrier to immunotherapy in solid cancers [8].

Both the IL-1 α receptor blocker anakinra and the IL-1 β receptor blocker canakinumab have been the subject of clinical trials and intense interest in the cancer field following news that the CANTOS trial unexpectedly showed that use of canakinumab to block IL-1 signaling was associated with a lower incidence and mortality from lung cancer [9,10]. Unfortunately, two key follow up studies, CANOPY I and CANOPY II, have failed to meet primary endpoints, and studies using anakinra, canakinumab, or newer IL-1 inhibitors remain ongoing. The study by Barisas and colleagues [4] may provide the additional insight needed to truly address immunosuppressive myeloid responses in cancer. In other words, blocking both IL-1 and LIF together may be much more effective than either alone. Future studies will determine whether antagonizing LIF or IL-1 or both is sufficient to reduce tumor progression either in the murine model or in humans.

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Author Contributions

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