Hematopoiesis is tightly orchestrated by hematopoietic stem cells (HSCs) in the bone marrow (BM) niche to ultimately produce mature myeloid and lymphoid blood cells. During infection, HSCs, which are predominantly dormant, briefly expand, proliferate, and differentiate in response to inflammatory signals such as pro-inflammatory cytokines. This process is called emergency myelopoiesis and plays a critical role in counterbalancing the loss of myeloid cells and replenishing them to control the infection, because myeloid cells generally have very low proliferative activity.

Macrophages are characterized by high plasticity and diversity, with two major phenotypes. M1 macrophages can augment helper T (Th)1 immune responses, resulting in strong microbicidal and tumoricidal activity, and M2 macrophages have an immunoregulatory function that helps to promote tissue remodeling and tumor progression. Under various pathogenic conditions, immature myeloid cells designated as myeloid-derived suppressor cells emerge and exert strong immunosuppressive functions. These cells are generated as a normal physiological response and are developed by stimulation with several tumor- or infection-derived cytokines, such as granulocyte macrophage colony-stimulating factor, granulocyte colony-stimulating factor, and macrophage colony-stimulating factor, but blocked from differentiating. Generally, tumor-bearing hosts and cancer patients have increased infiltration of immunosuppressive myeloid cells, such as M2 macrophages and myeloid-derived suppressor cells.

Interleukin (IL)-27, a member of the IL-6/IL-12 family of cytokines, is a multifunctional cytokine with both pro-inflammatory and anti-inflammatory properties. It promotes the early induction of Th1 differentiation and generation of cytotoxic T lymphocytes, but it inhibits the differentiation of naive CD4+ T cells into Th2 and Th17 cells and suppresses the production of pro-inflammatory cytokines. IL-27 is composed of Epstein-Barr virus-induced gene 3 and p28, and its receptor (R) consists of IL-27Rα and glycoprotein130, a common receptor subunit for the IL-6 family of cytokines. We first demonstrated the antitumor effects of IL-27 in 2004 using a mouse transplantable tumor model. Accumulating evidence obtained using several preclinical mouse and human tumor models indicates that IL-27 has potent antitumor activity against various types of tumors without apparent adverse effects; IL-27 acts via multiple mechanisms including cytotoxic T lymphocytes and natural killer cells, depending on the characteristics of individual tumors.

In addition, we first clarified its promoting effects on the expansion and differentiation of HSCs into myeloid progenitors by establishing IL-27-overexpressing transgenic mice. We also recently elucidated the protective effects of IL-27 on a mouse model of blood-stage malaria infection by promoting emergency myelopoiesis (Fig. 1A), as well as its antitumor effects through enhanced differentiation into antitumorigenic M1 macrophages (Fig. 1B).

The IL-27-transgenic mice show enhanced myelopoiesis with splenomegaly and extramedullary hematopoiesis in the spleen. Consistent with this, IL-27 together with stem cell factor synergistically and vigorously expands mouse BM cells for a long period. Among the various types of HSCs and progenitors in the BM, IL-27 and stem cell factor predominately act on long-term repopulating HSCs and promote their differentiation into myeloid progenitors, which have a unique potential to differentiate into migratory dendritic cells, neutrophils, and mast cells and less so into macrophages and basophils, but not into plasmacytoid dendritic cells, conventional dendritic cells, T cells, or B cells. Among the cytokines, IL-27 in synergy with...
stem cell factor has the strongest ability to augment the expansion of lineage Sca-1<sup>+</sup>c-Kit<sup>+</sup> (LSK) cells, which is a population highly enriched in HSCs, and their differentiation into myeloid progenitors retaining the same LSK phenotype. In the mouse model of blood-stage malaria infection, interferon (IFN)-γ production induced by IL-12 and phagocytic cells in the spleen play critical roles in controlling parasitemia to remove infected red blood cells. IL-27Ra-deficient mice show a greater increase in parasitemia during the early infection. The infection enhances IL-27 expression through IFN-γ production in the BM and spleen, and IL-27 then promotes the expansion and differentiation of LSK cells into myeloid progenitors, enhancing the production of neutrophils to control the infection (Fig. 1A). Thus, IL-27 is one of the few cytokines that directly acts on HSCs and promotes emergency myelopoiesis.

In tumor-bearing mice, IL-27 was revealed to augment the infiltration of myeloid cells into tumors. Intriguingly, however, deletion experiments of these myeloid cells and admixture experiments of them with parental tumors show that the IL-27-mediated tumor-infiltrating myeloid cells have reduced immunosuppressive activity and potent antitumor activity, rather than protumor activity as usually observed in non-treated tumor-bearing mice (Fig. 1B). The myeloid cells express a higher level of inducible nitric oxide synthase and directly kill tumors, mainly in a nitric oxide–dependent manner. In the BM of tumor-bearing mice, IL-27 increases the LSK cell population, which has an enhanced ability to differentiate into antitumorogenic M1 macrophages. These M1 macrophages then infiltrate into tumors and eradicate them.

In analogy with the effects of IL-27 on HSCs, some researchers have proposed the possibility of IL-27 inducing the expansion and differentiation of leukemic stem cells. Aberrant IL-27Ra signaling or IL-27 stimulation of leukemic stem cells that contain proliferative mutations like BCR/ABL may enhance myeloid cell growth, potentially leading to myeloproliferative neoplasms. However, IL-27-overexpressing transgenic mice never show any spontaneous development of leukemia during the entire life span under normal conditions. Moreover, supporting the effect of IL-27 on hematopoiesis in the BM, the p28 subunit of IL-27 is unique in having a polyglutamic acid domain, which is the acidic domain with hydroxyapatite-binding ability and bone tropism to bone sialoprotein. Therefore, therapeutic applications of IL-27 targeting hematologic tumor and solid tumor metastasis with bone tropism could prove beneficial.

Abbreviations

BM = bone marrow  
HSC = hematopoietic stem cell  
IFN = interferon  
IL = interleukin  
LSK = lineage Sca-1<sup>+</sup>c-Kit<sup>+</sup>  
R = receptor  
Th = helper T

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