Gut microbiota sustains hematopoiesis

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In this issue of Blood, Josefsdottir et al provide substantial evidence that commensal gut microbes regulate and sustain normal steady-state hematopoiesis.1

Hematopoiesis is regulated in part by extrinsic regulators, such as growth factors and cytokines, and in part by intrinsic epigenetic and transcriptional regulators that, in concert, orchestrate differentiation of stem cells via a series of progenitor cells into all types of fully mature blood cells.

In their study, Josefsdottir et al demonstrate that broad-spectrum antibiotic treatment of mice for >2 weeks depletes the intestinal microbial flora, which ultimately leads to a decrease in numbers of stem and progenitor cells in the bone marrow and concomitant anemia, leukopenia, and marked pan-lymphopenia. The authors provide substantial experimental evidence that these changes are not a toxic effect of antibiotics on hematopoietic cells, but rather are related to depletion of gut microbiota by antibiotic treatment.

Consistently, the effects of antibiotic treatment were phenocopied in germ-free mice and reversed by fecal microbiota transplantation.1

The molecular mechanisms by which commensal gut microbiota control proper immune function and hematopoiesis were recently shown to partially rely on microbial compounds such as lipopolysaccharides, which sustain steady-state production of neutrophils and their constitutive priming against bacterial infections through Toll-like receptor/MyD88-mediated signaling (see figure).2-4

Importantly, Josefsdottir et al were able to demonstrate that the effects of broad-spectrum antibiotic treatment on hematopoiesis were phenocopied in Stat1 knockout mice, suggesting that microbiota sustain steady-state hematopoiesis through activation of Stat1 signaling. However, further investigations are needed to unravel the type of cells experiencing direct or indirect activation of Stat1 signaling mediated by the commensal gut microbiota.

The novel findings by Josefsdottir et al extend the series of recent studies on host-microbe symbiosis, demonstrating that the gut microbiota is a critical extrinsic regulator of innate and adaptive immunity as well as hematopoiesis, which ultimately maintains the vigilance of the immune system against bacterial and viral infections (see figure).3,5,6 Consistently, perturbation of the balance and diversity in the composition of gut microbiota, referred to as dysbiosis, is associated with higher susceptibility to infections.5,6 Importantly, dysbiosis was also demonstrated to impair clinical

5. Lange RD, Minnich V, Moore CV. Effect of oxygen tension and of pH on the sickling and mechanical fragility of erythrocytes from patients with sickle cell anemia and the sickle cell trait. J Lab Clin Med. 1951;37(5):789-802.
response to a variety of cancer treatments including cyclophosphamide, platinum-based therapies, and immunotherapy. More recently, a single-center study even demonstrated that dysbiosis at the time of engraftment is an independent predictor of mortality after allogeneic stem cell transplantation. A follow-up study by the same research group further revealed that treatment of neutropenic fever after allogeneic stem cell transplantation with specific antibiotics (imipenem-cilastatin and piperacillin-tazobactam) leads to dysbiosis and increased graft-versus-host disease–related mortality.

In the context of these clinical observations, the intriguing data by Josefsdottr et al warrant further studies to investigate whether restoration of commensal gut microbiota in immunocompromised and antibiotic-treated cancer patients by fecal microbiota transplantation may improve clinical outcome after chemotherapy and immunotherapy as well as allogeneic stem cell transplantation.

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REFERENCES


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Comment on Alsuliman et al, page 740

T-cell immunity: strength out of quiescence?

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In this issue of Blood, Alsuliman et al describe a CD161+ T-cell population with selectively high toxin effluxing capacity through the MDR1 transporter that helps protect patients with acute myeloid leukemia (AML) during chemotherapy. T cells can confer protective immunity toward intracellular target proteins. Different subpopulations of T cells play a key role in distinct immune responses, such as directly killing virally infected or cancerous cells or inducing high-affinity antibody responses in B cells. To maintain protection, long-lived memory T cells are generated, which may persist throughout an individual’s lifespan. Immunotherapy has emerged as a way to treating viral disease and hematologic malignancies given alone or in combination with other types of therapy. Combining chemotherapy with a treatment that relies on functional active T-cell responses requires knowledge of T-cell populations that survive chemotherapy. Interestingly, patients receiving intensive chemotherapy for AML have a low risk of viral complications. Therefore, quiescent T cells with self-renewal capacity must be able to survive this toxic treatment. These quiescent T cells were initially generated after a first infection and may persist for a lifetime. The target-dependent T-cell response is controlled by the specificity of the T-cell receptor itself and by the wide heterogeneity and plasticity of CD4+ T helper (Th) cells.

Alsuliman et al studied long-lived pathogen-specific T cells to explore adaptive immune responses in patients undergoing chemotherapy for AML. The authors describe mechanisms underlying long-term persistence of antigen-specific T cells that are related to a subset of memory CD4+ T cells capable of effluxing cellular toxins, including rhodamine (Rho), through the multidrug efflux protein MDR1 (also known as P-glycoprotein and ABCB1). Drug-effluxing CD4+ T cells are characterized as CD161+CD95+CD45RA-CD127CD28+CD25+ cells (see figure) with a distinct chemokine profile and a Th1-polarized proinflammatory phenotype. For the T-cell response against viral and malignant target structures, effector function is crucial in combination with a strong expansion potential. The required effector functions of CD4+ Th cells are the Th1 cytokines such as interferon-γ, interleukin-2, and tumor necrosis factor.

Alsuliman et al describe vigorous proliferation and plasticity of the CD4+CD161+ Rho-effluxing T-cell subset. These cells are capable of self-renewal, maintaining their phenotypic and functional characteristics, and giving rise to CD161+ progeny. Multidrug effluxing CD4+CD161+ T cells are enriched within the viral-specific Th1 repertoire of healthy donors and AML patients. These cells also survive exposure to daunorubicin chemotherapy in vitro. Multidrug effluxing CD4+CD161+ T cells also resist chemotherapy-induced cytotoxicity in vivo and undergo significant expansion in AML patients who have been rendered lymphopenic after chemotherapy, contributing to the repopulation of antiviral immunity. These findings suggest that CD4+ CD161+ T cells with rapid efflux capacity contribute to the maintenance of viral-specific memory T cells during and after chemotherapy.

The described characteristics support the hypothesis that this T-cell subset is not only crucial for immune reconstitution during transient lymphopenia but is also a central player in the maintenance of CD4+ T-cell memory in healthy individuals and might be capable of expanding the pool of functionally diverse memory cells.

The identification of a specific long-lived CD4+ T-cell populace that is resistant to chemotherapy and can reconstitute preexisting immunity has important clinical implications, especially for vaccination and adoptive immunotherapy. It might allow monitoring of
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