something the World Health Organization Classification can consider at a future update. In the meantime, Wang and colleagues have provided a valuable contribution to the lymphoma literature by helping to define the natural history of an orphan entity.

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HEMATOPOIESIS AND STEM CELLS

Comment on Lee et al, page 1312

DNA-catching BM macrophages set hematopoiesis

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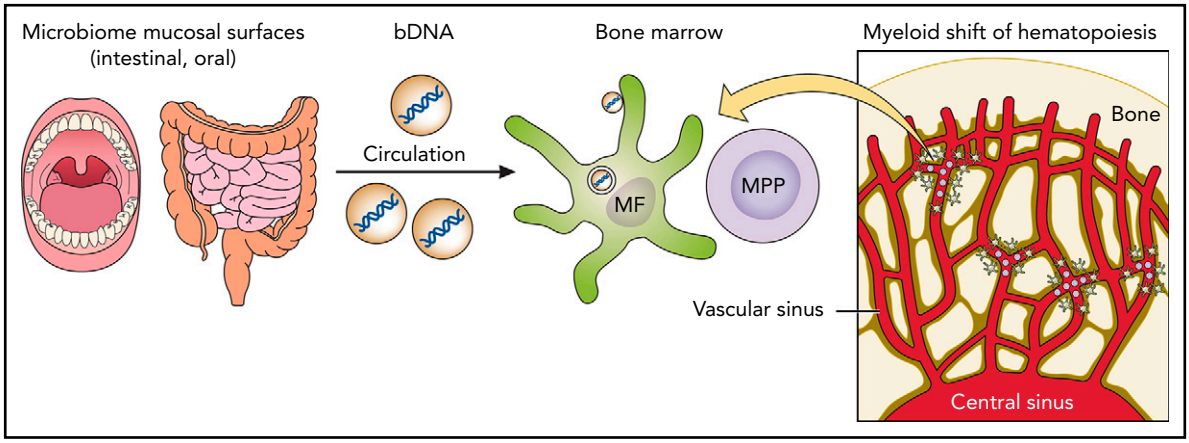
Hematopoiesis is well known to be affected by environmental factors, adjusting the balance of lymphoid and myeloid output according to peripheral needs.[1,2] Specifically, the bone marrow (BM), as a site of adult blood cell generation, has been shown to sense the gut microbiome composition and respond to dysbiosis associated with antibiotics treatment and numerous gastrointestinal disorders. In this issue of *Blood*, Lee et al[3] describe how this remote sensing is achieved and how the microbiota educate the immune system while maintaining critical steady-state myelopoiesis.[4]

The Lee et al study might well provide the critical missing link in our understanding of the communication circuit between the BM and the periphery (see figure). The authors identified a strategically positioned BM-resident macrophage population, defined by its perivascular location and MHCII, CD11b, CD11c, and CX3CR1 expression, that captures cell-free bacterial DNA (bDNA) from the blood circulation. They show that these macrophages are a prominent local homeostatic source of proinflammatory cytokines. Interestingly, macrophage production of tumor necrosis factor, interleukin-1 (IL-1), and IL-6, which have been collectively determined to affect hematopoiesis and immune cell lineage bias,[2] was abrogated in germ-free mice (ie, in the absence of microbiota). Moreover, the homeostatic cytokine production by the CX3CR1$^+$ macrophages observed in animals kept under conventional housing conditions was impaired when the cells were rendered deficient for the Toll-like receptor (TLR) signal transducer Myd88 or for Unc93b1, which is required for transport of nucleotide-sensing TLRs to endolysosomal compartments. Collectively, this establishes that the CX3CR1$^+$ BM macrophages use their endosomal TLRs to sense circulating bDNA and respond with local tonic, low-level cytokine secretion that impacts nearby progenitors and hematopoiesis.

The study by Lee et al may be a major breakthrough but it also raises many interesting new research questions. For example, What is the exact origin of the bDNA and how does it travel to the BM? As for the source of the bDNA, a 16S RNA analysis performed by the authors shows that, surprisingly, most of the material found in the BM macrophages is derived from *Proteobacteria*, a phylum that is underrepresented in the commensal intestinal microbiome, although it is more frequent during enteropathology. This could implicate a scenario in which certain bacterial species are more prone to contribute to the systemic bDNA pool than others. Alternatively, the bDNA that triggers the BM macrophages might originate from the commensal oral microbiota in which *Proteobacteria* are more prevalent. As for the way the bDNA gets to the BM, the authors invoke a cell-free route via extracellular vesicles (EVs) that have been shown to circulate in the blood and harbor microbiota-derived material, including peptidoglycans and bDNA.[5,6] In fact, using intravital microscopy, the authors show that the BM-resident macrophages seem to have a unique affinity for blood-borne bacteria-derived EVs.

Another interesting aspect of the work that deserves further exploration is the identity of the BM-resident cells that capture the bDNA. Unlike this author, Lee et al refrained from classifying these cells as dendritic cells (DCs) or macrophages, but refer throughout their study cautiously but wisely to CX3CR1$^+$ mononuclear cells.



The figure shows a link between commensals and hematopoietic homeostasis. CX3CR1$^+$ BM resident macrophages capture circulating bDNA wrapped in EVs, sense the cargo in their endosomal compartment with TLRs, and in response, produce proinflammatory cytokines that influence the abundance of hematopoietic precursors, such as multipotent progenitors (MPPs), and their output. MF, CX3CR1$^+$ macrophage.

Indeed, BM cells that are associated with perivascular niches and display an MHCII$^+$CD11b$^+$CD11c$^+$CX3CR1$^+$ phenotype had been reported earlier but were considered DCs because of their morphology, derivation from precursors with DC potential rather than monocytes, and superior ability to stimulate T cells.[7,8] Likewise, BM-resident macrophages have been implicated in the control of stem cell fates and hematopoiesis.[9,10] Here, one might ask: What's in a name? But it will be interesting to define how the bDNA catchers relate to these other reported cell populations and whether they harbor additional activities in the BM. Further dissection of the BM DC and macrophage compartment and assignment of specific functions will likely benefit from single-cell transcriptomics, as well as the development of binary Cre recombinase systems to better target myeloid cell subpopulations.

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LYMPHOID NEOPLASIA

Comment on Gao et al, page 1346

ECP in the spotLIGHT

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In this issue of *Blood*, Gao et al demonstrate that extracorporeal photopheresis (ECP), when used as monotherapy in the first-, second-, or third-line therapy of patients with Sézary syndrome (SS) or erythrodermic mycosis fungoides (eMF), leads to prolonged disease control, as demonstrated by a median time to next treatment (TTNT) of 42 months and is superior to alternative non-ECP therapies used in the first-line setting (median TTNT, 3.5 months).[1]

In contrast to early-stage mycosis fungoides (MF), which is largely managed with skin-directed therapies ("lotions and light"), patients with late-stage disease, including SS and eMF, benefit from a smorgasbord of systemic therapeutic options. Although largely incurable, immunomodulatory therapies, including interferon-α and ECP, may be associated with prolonged and durable remissions (reviewed in Wilcox[2]). In stark contrast, and as previously demonstrated by this same group of investigators,[3] responses achieved with conventional chemotherapeutic agents are transient and rarely durable.

ECP, as pioneered by Edelson et al,[4] passes leukopheresis-enriched peripheral