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# Diabetes Gets on the Nerves of the Bone Marrow Niche

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Diabetes is one of the major risk factors of coronary artery disease and chronic heart failure in the Western world (1). Currently, there are ~28 million patients at age 20 years and older affected by diabetes in the U.S. alone with an annual incidence of 180,000 new cases. Moreover, 186,000 individuals, younger than 20 years of age, have diabetes, and each year ~15,000 new patients are diagnosed with type 1 diabetes (1). The systemic nature of the metabolic derangement caused by diabetes inevitably results in comorbidities in several organs. Diabetes is the most common cause of neuropathy, which, in turn, represents its most frequent complication, affecting up to 50% of diabetic patients (2,3). A particularly severe form of diabetic neuropathy consists of the impairment of the sympathetic and parasympathetic divisions of the autonomic nervous system. Diabetic autonomic neuropathy (DAN) can affect the cardiovascular, genitourinary, and gastrointestinal organs. Cardiovascular autonomic neuropathy is an early and frequent complication of diabetes, comprising 7–15% of newly diagnosed individuals and 90% of chronically ill patients (4). In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, cardiovascular autonomic neuropathy has been shown to double the risk of death in diabetic patients (5).

In this issue, the findings discussed in the study by Albiero et al. (6) provide novel insights for the current understanding of the biology of DAN. The impact of DAN on the bone marrow (BM) and its niches is largely unknown. Stem cell niches are anatomical compartments constituted by cellular and extracellular components, which integrate local and systemic cues for the control of stem cell fate (7). The BM niche is a functional entity with a high degree of plasticity necessary for rapid adaptation to the needs of the organism. With aging and diseases, BM niches undergo extensive remodeling, altering the properties of resident stem cells and early committed progenitors. Deregulation of niche homeostasis creates abnormal sites of cell renewal, lineage specification, and mobilization, promoting global changes in BM function with systemic repercussion.

The retention of progenitor cells in BM niches is primarily dictated by the interaction between the CXCR4 receptor expressed on the surface of the cells and the stromal cell–derived factor 1 (SDF-1) ligand released by the neighboring supporting cells (7). The mechanism by which the mobilizing agent granulocyte colony–stimulating factor (G-CSF) favors the translocation of progenitors to the peripheral blood was thought to implicate mainly the disruption of the SDF-1–CXCR4 axis by reducing the expression of both receptor and ligand. However, the identification of the "nervous niche" has led to the discovery that G-CSF function involves signals through the sympathetic nervous system, which affect the activity of the hematopoietic niche and the egress of BM cells (BMCs) (8,9). The study by Albiero et al. supports the notion that BM innervation is a crucial regulator of homing and migration of hematopoietic and endothelial progenitor cells. The interplay between the BM and its nervous components involves an indirect effect of the sympathetic terminations on osteoblasts and osteoclasts and a direct effect on the neurotransmitter receptors abundantly expressed in resident cells (10). On this basis, the intriguing theory of the regulatory "brain-bone-blood triad" was developed to emphasize the relevance of the "dynamic crosstalk between bone remodeling, hematopoietic progenitors and their evolving niches via neurotransmitter signaling" (11). Pathological conditions may interrupt the stream of information from the nervous system to the BM niches (Fig. 1).

A significant reduction in the number of BM-derived circulating cells has frequently been described in diabetic patients and animal models of the human disease (12). Albiero et al. echo these clinical and experimental findings, but add a new layer of complexity to the understanding of the mechanisms responsible for the poor mobilization of BMCs with diabetes. In a compelling

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COMMENTARY

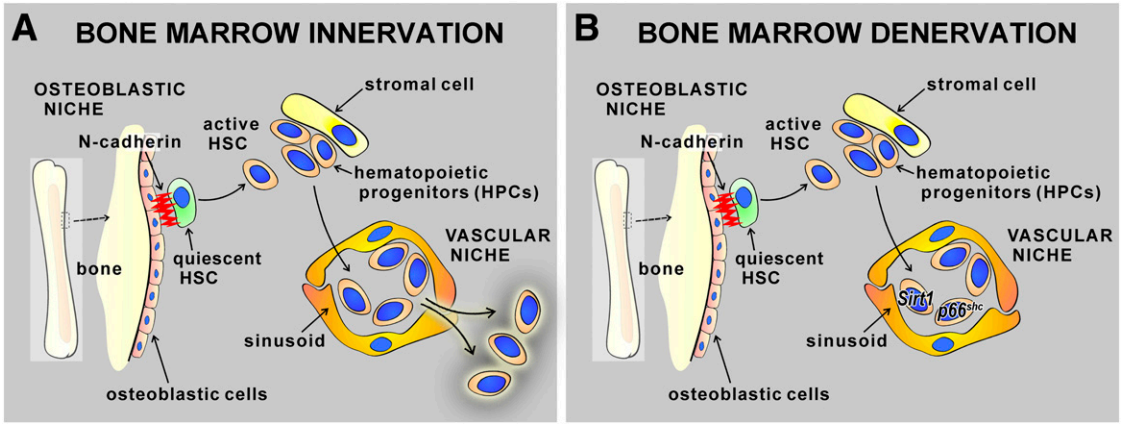


**Figure 1**—Shown schematically, two distinct niches are present in the BM. The environment of the osteoblastic niche preserves the quiescence of HSCs. Following activation, HSCs undergo early commitment forming hematopoietic progenitor cells (HPCs) and migrating to vascular niches. The integrity of BM innervation (*A*) ensures effective migration of HPCs from the niche to the peripheral circulation. In contrast, BM denervation (*B*) induces retention of HPCs within the niche. HPCs are characterized by upregulation of *p66Shc* and downregulation of *Sirt1*.

manner, the expression of two life span–related genes, *p66Shc* and *Sirt1*, was shown to regulate the migration of BMCs from their site of origin to the peripheral blood in mice with type 1 and type 2 diabetes. Additionally, a model of chemically induced sympathectomy was developed to mimic BM denervation. The upregulation of *p66Shc* and the downregulation of *Sirt1* in circulating mononuclear cells harvested from patients suffering from DAN mirror the findings obtained in the animal groups.

Targeted mutations of the *p66Shc* gene decrease the generation of reactive oxygen species (ROS), increase the resistance of cells to oxidative stress, and prolong life span in mice. Because of these characteristics, mice carrying a deletion of the *p66Shc* gene ($p66Shc^{-/-}$) have been extremely relevant to collect evidence supporting the hypothesis that oxidative stress with diabetes alters organ homeostasis (13). In the study by Albiero et al., the activity of the sympathetic system was identified as novel upstream regulator of *p66Shc* expression. Preservation of BM innervation in diabetic $p66Shc^{-/-}$ mice resulted in the correction of the defective migration of BMCs and opposed the downregulation of *Sirt1*. Diabetic animals crossed with $p66Shc^{-/-}$ mice responded effectively to G-CSF with mobilization of hematopoietic stem cells (HSCs) and endothelial progenitor cells (EPCs).

Whether deletion of *p66Shc* leads to an enhanced formation of free radicals in BMCs was not established, leaving unanswered the question of whether ROS accumulation is a determining factor of the defects in BMC migration. However, oxygen toxicity and DNA damage induce telomere shortening, which is a negative modulator of the migration of stem cells, opposing their egress from the niches (14). As shown in the study by Albiero et al. (6), hematopoietic-restricted $Sirt1^{-/-}$ mice recapitulate the diabetic stem cell "mobilopathy," while overexpression of *Sirt1* results in BMC mobilization, overcoming the detrimental influence of diabetes and sympathectomy on circulating cells.

The effects of BM denervation on the retention of BMCs were tested in the current study in clinically relevant conditions, including the administration of G-CSF and tissue ischemia (6). G-CSF treatment is the protocol currently employed for BMC mobilization in patients. However, its efficacy in animals with DAN was significantly compromised. To overcome this obstacle, CXCR4 antagonists were administered to sympathectomized mice, obtaining effective migration of BMCs from the nervous niches into the circulation. This strategy, which promotes pharmacological inhibition of the interaction of CXCL12 with its receptor CXCR4, is independent from the loss of integrity of BM innervation and may be successful in diabetic patients.

The motile phenotype of circulating HSCs and EPCs reflects their ability to migrate to distant tissues and engraft and differentiate into the cell lineages of the recipient organ. In the study by Albiero et al., cells of BM origin localized primarily in the vessel wall and initiated a process of vasculogenesis, which ameliorated distal perfusion in hind-limb ischemia.

An interesting aspect of the mechanisms regulating niche homeostasis was addressed in the current study. Within the niches, stem cell–autonomous processes act in combination with signals derived from the supporting cells. In addition to downregulation of *Sirt1* and upregulation of *p66Shc*, DAN was found to be associated with a rearrangement of the pattern of expression of niche adhesion molecules. This molecular adaptation favors the retention of BMCs in the tissue milieu, opposing the detachment of primitive cells from the surrounding stromal cells. In view of the reciprocal cross talk between stem cells and supporting cells, the alterations in gene

profiling of adhesion molecules in BMCs is likely to determine functional changes in the mesenchymal cell pool. This intriguing question may be addressed in future studies to establish whether DAN affects directly the behavior of stromal cells or whether this phenomenon is mediated by dysfunctional stem cells.

As stated, whether metabolic dysregulation per se affects BMC migration independently from DAN remains to be defined. However, the results in the three animal models studied are consistent with the relevance of BM neuropathy for the release of BMCs to the peripheral blood. Collectively, the data obtained by Albiero et al. (6) strongly indicate that diabetes induces changes in the microenvironment of the BM niches and promotes alterations of the gene expression profile in BMCs, two critical variables contributing to the poor motility of HSCs and EPCs in patients with DAN. Based on these findings, novel therapeutic targets for the treatment of this form of neuropathy and its complications have been identified. Neurotransmitters and alternative mobilizing protocols may be used as novel approaches to enhance proliferation and migration of BMCs, favoring the repopulation and repair of damaged tissues with vasculogenic cells.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

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