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Rewiring the Niche: Sympathetic Neuropathy Drives Malignant Niche Transformation

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In recent years, it has become increasingly evident that hematological malignancies can alter their microenvironment, but the therapeutic implications of these changes and potential targets have not been well characterized. Recent findings now describe how sympathetic neuropathy can drive malignant transformation of the hematopoietic stem cell niche in hematopoietic malignancies.

Hematopoietic stem and progenitor cells (HSPCs) reside within highly specified compartments of the bone marrow (BM). These "niches"—differentiated by their physical location within the marrow, the stromal cells forming the compartment and the HSPC maintenance factors present within the niche microenvironment—can regulate HSPC proliferation, dormancy, and migration. Thus, they maintain homeostasis and facilitate dynamic responses to challenges to the hematopoietic system. The perivascular HSPC niche refers to a region populated by stromal cells that include CXCL12 reticular cells, Nestin+ MSCs, and LepR+ MSCs expressing multiple soluble and membrane-bound factors that regulate HSPC self-renewal and retention within the niche (Frenette et al., 2013; Doan and Chute, 2012). This niche is also characterized by high levels of sympathetic nerve fiber innervation that contributes to the regulation of HSPC BM trafficking (Katayama et al., 2006). The osteoblastic or endosteal niche is an alternate BM compartment characterized by osteolineage cells and the localized expression of regulatory factors including osteopontin (OPN) and additional niche components that mediate HSPC localization and stem cell pool size (Lévesque et al., 2010).

In the malignant context of leukemia or myeloproliferative neoplasms (MPN), disease progression has been shown to induce wide-scale morphological changes within the niche compartments, including remodeling of bone and increased vascularity. Leukemic cells have been shown to alter the niche in a manner that affects normal HSPC migration, pool size, and differentiation (Colmone et al., 2008; Hu et al., 2009). These changes to niche anatomic and molecular architecture that are induced by leukemic or MPN cells have also been shown to impact survival and expansion of the malignant clones (Boyerinas et al., 2013; Schepers et al., 2013).

In a recent *Nature* publication, Arranz et al. (2014) describe alterations arising within the HSPC niche that contribute to MPN progression. A number of mutations occurring in HSPCs, including that of BCR-Abl and constitutively active Janus Kinase 2 (JAK2), are known to drive MPN HSC and progenitor expansion, but this study describes how MPN-induced sympathetic neuropathy in the perivascular niche propels JAK2 mutant MPN pathogenesis. Through analyzing MPN patient BM biopsy samples, the authors observed a significant loss of Nestin+ perivascular niche cells and sympathetic nervous system (SNS) fibers, which was recapitulated in JAK2 mutant mice. Interleukin-1β (IL-1β) produced by MPN cells was shown to drive the destruction of Schwann cells that support the SNS fibers and was followed by the apoptotic loss of Nestin+ cells in mice and a reduction in micorenvironmental levels of HSPC maintenance factors, including CXCL12. This altered niche results in peripheral mobilization of HSPCs and accelerated BM expansion of MPN cells. This effect could be inhibited by the employment of neuroprotective agents or the treatment of mice with selective β3 adrenergic receptor agonists; i.e., the prevention of sympathetic neuropathy or the replacement of the adrenergic signaling to Nestin+ MSCs. These results indicate that the destruction of sympathetic nerve fibers in the perivascular niche by MPN cells themselves induces Nestin+ MSC apoptosis, HSPC niche alteration, and MPN pathogenesis.

In a study in this issue of *Cell Stem Cell*, Hanoun et al. (2014) identified a similar role for neoplastic niche alteration through sympathetic neuropathy; however, they performed their analyses using an aggressive MLL-AF9 acute myelogenous leukemia (AML) model. Ablation of catecholaminergic neurons by 6-Hyroxydopamine resulted in greater BM infiltration of leukemic stem cells (LSCs or L-GMPs: IL-7R− Lin− GFP+ c-Kit+ CD-34^{lo} FcRII/III^{HI}) and decreased survival time in leukemic mice. Catecholaminergic nerve fibers were shown to be depleted in Nestin+ perivascular niche regions in leukemic versus control mice, indicating that SNS neuropathy coincided with AML progression. SNS denervation of the HSC niche by AML also resulted in significant changes in mesenchymal stem/progenitor cell (MSPC) numbers and differentiation status. The Nestin+ MSPC population in leukemic mice was expanded and had an increased tendency toward osteoblastic lineage differentiation but with limited development into mature osteoblasts. MSPCs isolated from AML mice also expressed lower levels of factors associated with HSPC homing and retention (VCAM-1, CXCL12, SCF, and Angpt1) but increased levels of OPN. Moreover, HSPCs isolated from AML mice had decreased BM repopulation capacity while increased numbers of HSPCs were present in the peripheral blood and spleen compared to those in control mice. These findings indicate that AML colonization of the BM significantly alters the HSPC niche, compromising its ability to retain functional HSPCs.

To address the functional effects of SNS neuropathy in AML, the authors treated leukemic mice with adrenergic β2 and β3 receptor antagonists. β2, but not β3, adrenergic blockade increased phenotypic LSC numbers in mice and reduced survival. In comparison, treatment with a β2 adrenergic receptor agonist decreased LSC numbers and resulted in a trend toward increased survival. The presence of β2 receptors on MLL-AF9 leukemic cells and their proliferative response to adrenergic stimulation in vitro, however, suggest that a therapeutic approach to SNS neuropathy in AML may not be straightforward.

Both studies discussed in this Preview report on the significance sympathetic neuropathy plays in malignant cell co-opting of HSPC niches during disease progression in AML and MPN. While loss of catecholaminergic innervation is central in both diseases, different sequelae are observed within the niche. MPN-induced neuropathy alters the perivascular niche through induction of apoptosis in Nestin+ MSCs, disrupting normal HSPC niche regulation and allowing accelerated MPN progression. In AML, neuropathy induces an increase in the number of Nestin+ MSCs, which display an altered osteoblastic lineage potential and a reduction in HSC niche supportive factors. Also, in MPN a clear therapeutic strategy to inhibit progression is identified by Arranz et al. (2014) through either the use of neuroprotective agents to prevent MPN-induced neuropathy or the replacement of lost β3 adrenergic signaling to Nestin+ MSCs via treatment with synthetic agonists. In AML, Hanoun et al. (2014) report that SNS neuropathy and LSC expansion is mediated by the β2, not β3, adrenergic receptor; however, the proliferative response of β2 receptor+ AML cells to direct adrenergic stimulation complicates a therapeutic strategy. Overall, these studies provide significant new insight into the role of the SNS in regulating the HSPC niche and how circumventing its regulatory capacity is critical for malignant niche transformation in both MPN and AML. They also highlight the complexity of the HSPC niche and the unexpected chain of events that can ensue from crosstalk amidst its diverse constituents.

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Ch-Ch-Changes: Hormones Link Stem Cell Differentiation with Metabolic Flux

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Emerging evidence strongly suggests that stem cells and their differentiated progeny display distinct metabolic profiles, but how metabolic changes are coupled with organogenesis has remained unclear. Homem et al. (2014) now reveal a hormone-dependent pathway that couples metabolic changes with stem cell differentiation, thereby terminating neurogenesis in the *Drosophila* brain.

Work in the past few years has revealed fundamental differences in metabolic regulation between stem cells and differentiated cells, with proliferating stem cells relying more on glycolysis and differentiating cells relying more on oxidative phosphorylation (Folmes et al., 2012). Similar to stem cells, cancer cells predominantly rely on aerobic glycolysis, termed the "Warburg Effect," for energy generation. Thus, understanding the metabolic changes occurring during