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The functional interplay between systemic cancer and the hematopoietic stem cell niche

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ABSTRACT

Hematopoietic cells are increasingly recognized as playing key roles in tumor growth and metastatic progression. Although many studies have focused on the functional interaction of hematopoietic cells with tumor cells, few have examined the regulation of hematopoiesis by the hematopoietic stem cell (HSC) niche in the setting of cancer. Hematopoiesis occurs primarily in the bone marrow, and processes including expansion, mobilization, and differentiation of hematopoietic progenitors are tightly regulated by the specialized stem cell niche. Loss of niche components or the ability of stem cells to localize to the stem cell niche relieves HSCs of the restrictions imposed under normal homeostasis. In this review, we discuss how tumor-derived factors and therapeutic interventions disrupt structural and regulatory properties of the stem cell niche, resulting in niche invasion by hematopoietic malignancies, extramedullary hematopoiesis, myeloid skewing by peripheral tissue microenvironments, and lymphopenia. The key regulatory roles played by the bone marrow niche in hematopoiesis has implications for therapy-related toxicity and the successful development of immune-based therapies for cancer.

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Contents

1. Introduction

Hematopoietic stem cells (HSCs) respond to cues from distant stress such as infection and wounding by entering a proliferative phase that ceases upon resolution of the injury (Wilson et al., 2008). Tumors can elicit a wounding response, and patients with breast cancer whose tumors express a "wounding response signature" have markedly diminished overall and metastasis-free survival (Chang et al., 2005). Yet, unlike a wound, tumors do not "heal," and activated HSCs cannot return to a quiescent state. Here, we discuss how hematologic

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BM, bone marrow; CML, chronic myelogenous leukemia; G-CSF, granulocyte colony stimulating factor; HIF-1α, hypoxia-inducible factor -1α; HSC, hematopoietic stem cell; IL, Interleukin; LT-HSC, long-term hematopoietic stem cell; MSC, mesenchymal stem cell; OBC, osteoblastic cells; OPN, osteopontin; PTH, parathyroid hormone; VEGF, vascular endothelial growth factor.

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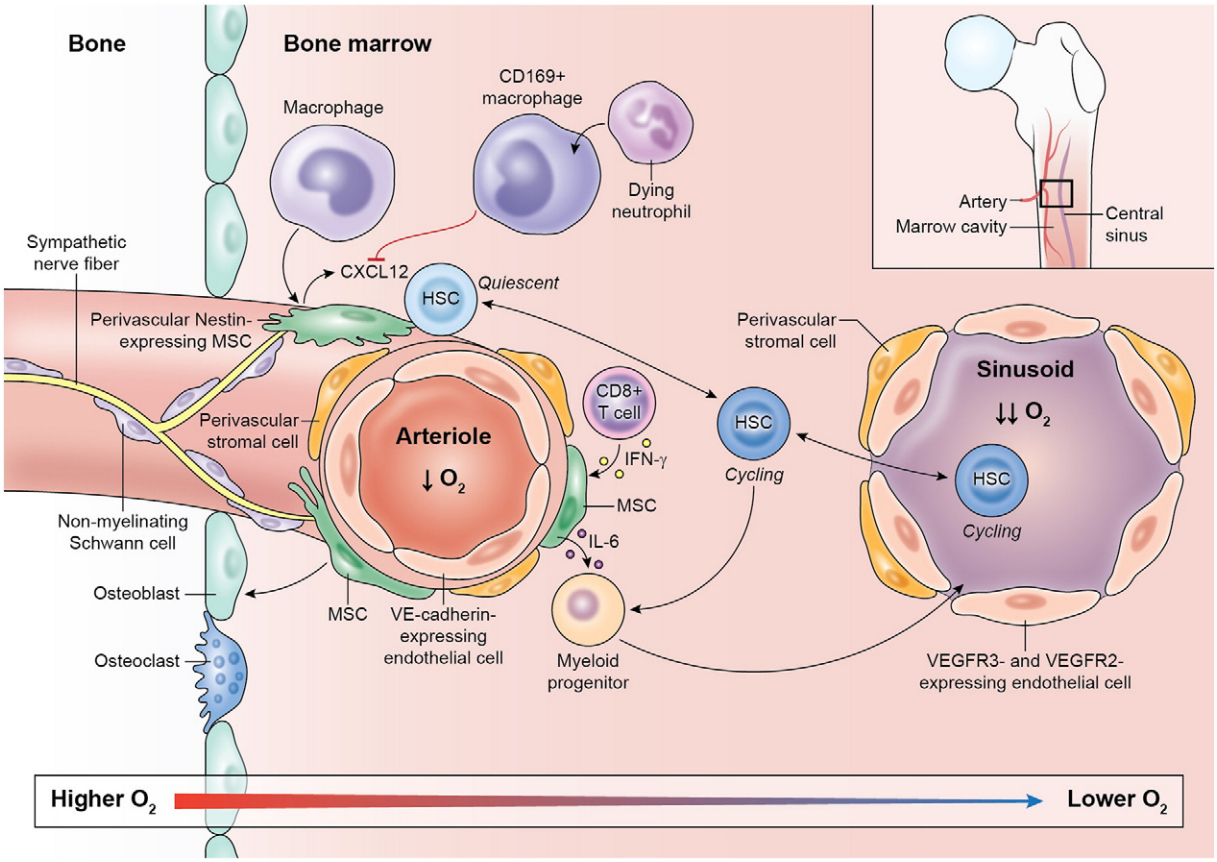

Fig. 1. Structural and regulatory properties of the HSC niche. The endosteum is formed from osteoblasts, osteoprogenitor cells, and osteoclasts. This creates the "osteoblastic niche" and quiescent HSCs are found proximal to this region. Arterial vessels surrounded by a thin layer of smooth muscle cells and nestin-expressing perivascular MSCs enter the bone and branch into smaller arterioles that run adjacent to the endosteum. Non-myelinating Schwann cells ensheath sympathetic nerve fibers that run alongside arterioles, innervating smooth muscle cells and nestin-expressing perivascular MSCs. Highly enriched HSCs are localized to the abluminal surface of VE-cadherin-expressing endothelial cells. Arterioles drain into sinusoids that contain wide intercellular clefts that allow for cell migration. Oxygen levels decrease as blood vessels travel deeper into bone. $CD169^+$ macrophages contribute to HSC retention by promoting CXCL12 production from MSCs. However, upon engulfing aged neutrophils that home back to the bone marrow, CXCL12 production is inhibited, permitting HSC mobilization and contributing to circadian oscillations of HSCs. Interferon gamma-expressing cytotoxic $CD8^+$ T cells stimulate myelopoiesis by inducing MSCs to secrete IL-6, linking adaptive and innate immune responses.

Table 1
Factors that impact the HSC niche in the setting of cancer.

Growth Factors	Source	Effect on bone marrow	Reference
VEGF	Tumor	Reduction of bone marrow sinusoidal vessels	O'Donnell et al., 2016
Notch ligand	Osteoblasts; Endothelial cells	ALL competes with HSCs for ligand, reducing HSC repopulation potential	Wang et al., 2016

Cytokines	Source	Effect on bone marrow	Reference
IL-1	AML	Increases expression of G-CSF and GM-CSF from endothelial cells	Griffin et al., 1987
IL-6	MSCs; endothelial cells	Increased expression due to CML or tumor-derived exosomes promotes myeloid lineage differentiation.	Li et al., 2016
IL-8/CXCL-8	bone marrow stromal cells; tumor	Increased expression due to tumor-derived exosomes results in HSC mobilization	Li et al., 2016; Corrado et al., 2014
CXCL12	bone marrow stromal cells; endothelial cells	Reduced expression impairs HSC homing to niche.	Zhang et al., 2012; Hanoun et al., 2014
Kit ligand/SCF	nestin-expressing mesenchymal stem and progenitor cells	Decreased expression results in loss of HSC repopulation potential	Hanoun et al., 2014; Huan et al., 2015
MIP-1	Bone marrow macrophages	Increased expression due to CML	Zhang et al., 2012
G-CSF	nestin-expressing mesenchymal stem and progenitor cells; tumor cells	Decreases expression of HSC homing and survival factors	Mendez-Ferrer et al., 2010

Other	Source	Effect on bone marrow	Reference
Adrenergic signaling	Sympathetic nerve fibers; Schwann cells; nestin-expressing MSCs	Sympathetic neuropathy results in skewing of perivascular mesenchymal stem and progenitor cells to immature osteoblasts.	Hanoun et al., 2014
Angiopoietin-1	Osteoblasts; nestin-expressing MSCs	Reduced expression impairs HSC quiescence	Hanoun et al., 2014
Osteopontin	Osteoblasts; secreted by tumor	OPN from tumor activates bone marrow and enhances metastatic potential of tumors.	McAllister et al., 2008; Lund et al., 2013