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# Bone marrow niches and HSC fates

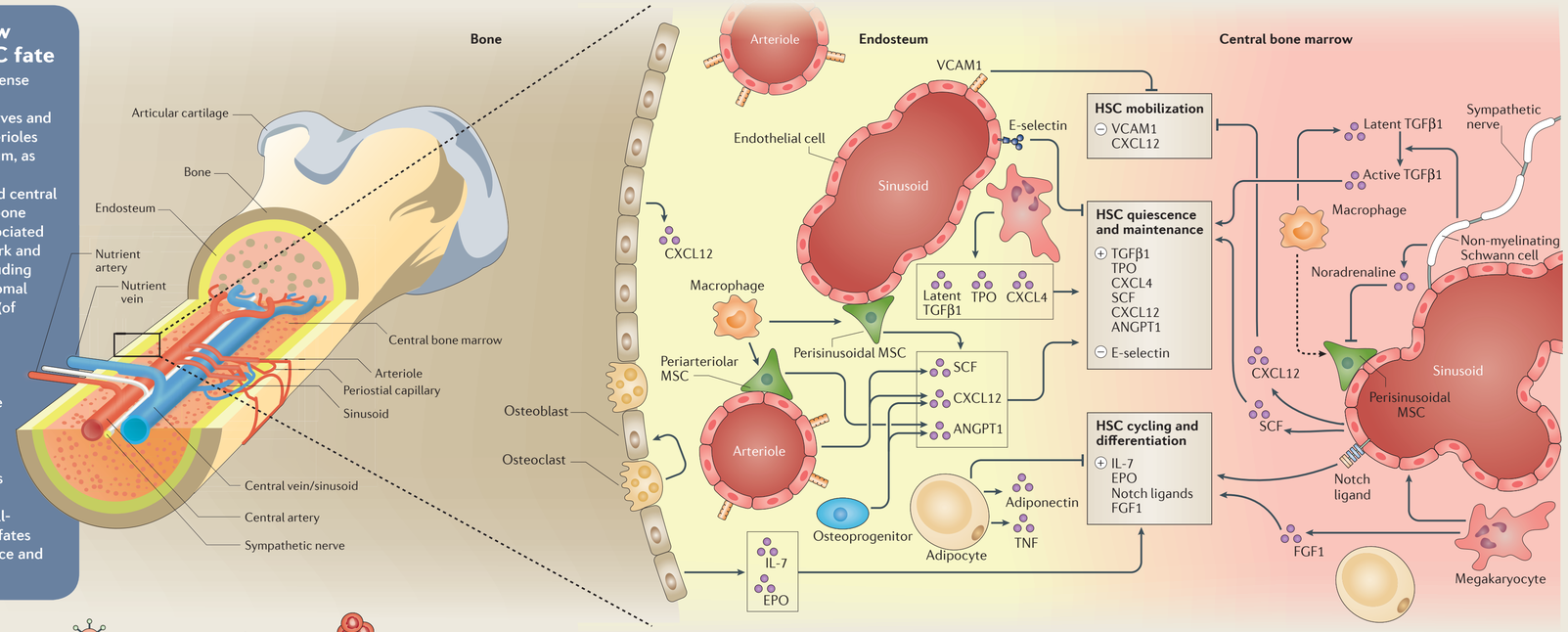
Evgenia V. Verovskaya, Timothy B. Campbell and Emmanuelle Passegué

Self-renewing and multipotent haematopoietic stem cells (HSCs) generate all mature blood cells. Adult HSCs exist in highly specialized bone marrow niches. These niches have crucial roles in regulating the fate of HSCs in terms of quiescence, mobilization into the peripheral blood and differentiation in response to steady-state and emergency cues. HSC fate is influenced by diverse types of stromal and haematopoietic cells that make up the bone marrow niche and provide signals in the form of soluble factors, direct cell–cell contact and cell-surface ligands. In stress conditions, such as during an inflammatory response, bone marrow niches respond by regulating the balance of downstream HSC fates. In the case of myeloid malignancies, bone marrow niches can be remodelled to create an environment that supports malignant stem cells but impairs the maintenance of normal HSCs. Understanding the signalling pathways of the bone marrow niche will aid the therapeutic use and targeting of HSCs, as well as provide more general insights into stem cell regulation and the function and composition of stem cell niches.



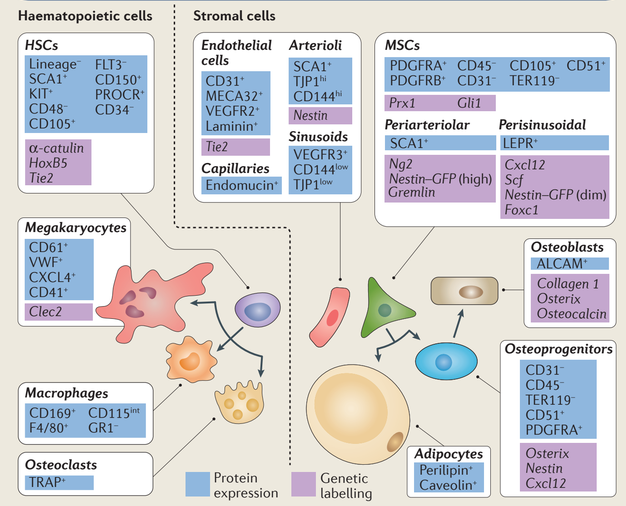
## Diverse bone marrow niches influence HSC fate

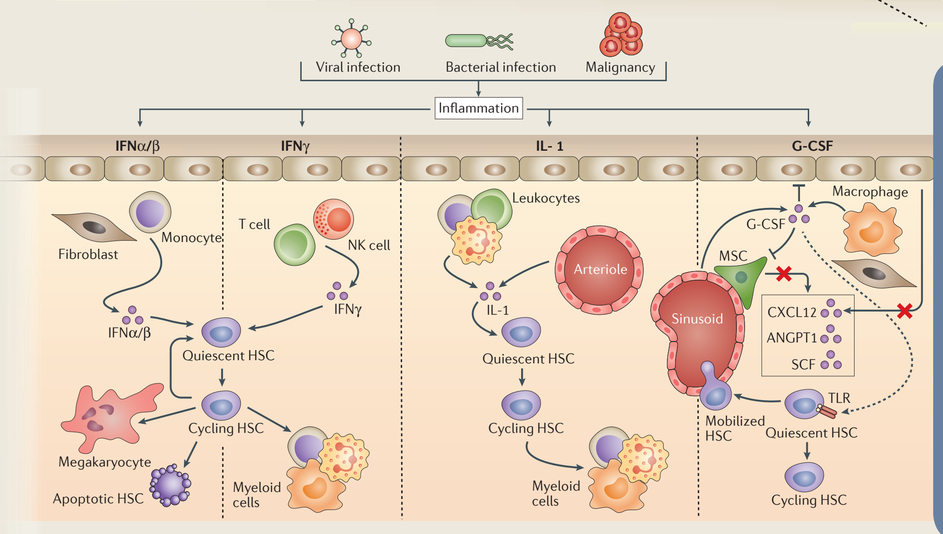
The bone marrow contains a dense neurovascular network that is innervated by sympathetic nerves and includes an enrichment of arterioles and capillaries in the endosteum, as well as large sinusoids located throughout the endosteum and central bone marrow cavity. Cellular bone marrow niches are closely associated with this neurovascular network and contain stromal elements including perivascular mesenchymal stromal cells (MSCs), endothelial cells (of arterioles, capillaries and sinusoids), differentiated osteoprogenitors and adipocytes. Haematopoietic cells of the bone marrow niche include megakaryocytes, macrophages and osteoclasts. These diverse cell types provide crucial signals to HSCs in the form of soluble factors, direct cell–cell contact and cell-surface ligands that influence fates such as mobilization, quiescence and differentiation.




## Identification of bone marrow niche cell types in mice

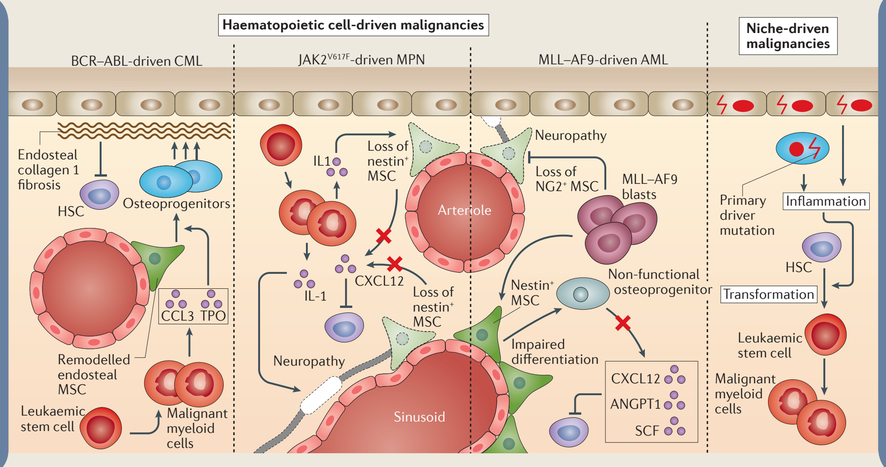
Bone marrow niche cells have been characterized by protein expression (cell-surface and intracellular), by genetic labelling and by lineage tracing. Expression patterns often correlate with specialized locations of niche cells in vascular bone marrow niches (capillaries, arterioli or sinusoids), particularly for MSCs and endothelial cells.




## Stress signals alter HSC fates

Diverse stressors and insults to the bone marrow, such as bacterial and viral infection and malignancy, create an inflammatory milieu that controls HSC fate via cell-surface receptors. Inflammatory factors can act on HSCs and their downstream progenitors through various mechanisms that are illustrated by the prototypical examples of type I and type II interferons (IFNs; IFNα/β and IFNγ, respectively), IL-1 and G-CSF. IFNs are produced preferentially by haematopoietic cells and act directly on HSCs to direct downstream differentiation and proliferation. IL-1 is produced under stress conditions by stromal and haematopoietic cells and acts directly on HSCs to drive an emergency myeloid response. G-CSF is produced by stromal and haematopoietic cells and acts indirectly on HSCs by downregulating the production of stromal cell-derived factors, which affects HSC quiescence and mobilization, and by the induction of TLR signalling, which leads to HSC proliferation.




## The active roles of bone marrow niches in malignancy

Bone marrow niches have an active role in the initiation and progression of myeloid malignancies. In BCR–ABL-driven CML, remodelled endosteal MSCs differentiate to osteoblast lineage cells that deposit collagen I at the endosteal surface, creating a hostile environment for normal HSCs. In JAK2$^{V617F}$-driven MPN, neuropathy and loss of nestin$^+$ MSCs are hallmarks of disease progression, mediated by IL-1-driven inflammation. In MLL–AF9-driven AML, sympathetic neuropathy leads to the depletion of periarteriolar NG2$^+$ MSCs but expands the population of remodelled osteoblast-primed nestin$^+$ MSCs through a mechanism dependent on β-adrenergic signalling. Primary driver mutations in bone marrow niche cells, particularly osteoprogenitor cells, can initiate myeloid malignancies within the haematopoietic compartment by establishing an inflammatory milieu.



**Abbreviations**
ALCAM, activated leukocyte cell adhesion molecule; AML, acute myeloid leukaemia; ANGPT1, angiopoietin 1; *Clec2*, C-type lectin domain family 2; CML, chronic myeloid leukaemia; CXCL, CXC-chemokine ligand; EPO, erythropoietin; FGF1, fibroblast growth factor 1; FLT3, Fms-related tyrosine kinase 3; *Foxc1*, Forkhead box c1; GFP, green fluorescent protein; G-CSF, granulocyte colony- stimulating factor; IL, interleukin; LEPR, leptin receptor; MPN, myeloproliferative neoplasm; PDGFRA, platelet-derived growth factor receptor A; PROCR, protein C receptor; SCF, stem cell factor; TGFβ1, transforming growth factor β1; TJP1, tight junction protein 1; TLR, Toll-like receptor; TNF, tumour necrosis factor; TPO, thrombopoietin; TRAP, tartrate-resistant acid phosphatase; VCAM1, vascular cell adhesion molecule 1; VEGFR, vascular endothelial growth factor receptor; VWF, von Willebrand factor.

**Affiliations**
Evgenia V. Verovskaya, Timothy Campbell and Emmanuelle Passegué are at the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California San Francisco, California 94143, USA. Evgenia V. Verovskaya and Emmanuelle Passegué are relocating to the Columbia Stem Cell Initiative, Columbia University Medical Center, New York 10032, USA.

Correspondence to E.P.
e-mail: ep2828@cumc.columbia.edu
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