

MICROENVIRONMENTAL CONTROL OF HEMATOPOIETIC STEM CELLS: IMPLICATIONS FOR REGENERATION AND THERAPY

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ABSTRACT

The hematopoietic stem cells are concentrated in localized bone-marrow micro-environmental niches that tightly regulate the balance between quiescence, self-renewal as well as differentiation. This review systematically covers the complicated biological and physical determinants of hematopoietic stem cell fate. First, we discuss the most significant input of physical and mechanical signals, including stiffness of the extracellular matrix and sheer force of blood flows, along with the high level of spatial heterogeneity of the endosteal and perivascular compartments. Besides, we highlight the high impact of the critical chemical signals, such as metabolic programming, cytokines and trophic factors that interact in a synergistic manner with cellular interactions, which are mediated by mesenchymal stromal cells, osteoblasts, and immune constituents. The fundamentals of molecular pathways that are central, especially the Notch and Wnt signaling and their influence on the epigenome are outlined to demonstrate the processes through which the hemopoietic stem cell respond to the environmental stimuli. Most importantly this review mentions pathological perturbation of the niche which contrasts both the inflammatory degradation that accompanies the aging microenvironment termed inflammaging and the subverted, protective milieu found in leukemic niches. Finally, a wrap up on the combination of the basic biology with the translational therapies is also provided and this gives an overview of new developments in the field of bioengineered scaffold and microfluidic bioreactors and niche-specific agents like CXCR4 antagonists. Through explaining the interaction between these complex micro-environmental factors, it can be assumed that future studies can optimize personalized niche modeling, scale up ex-vivo stem-cell growth, and develop next-generation precision therapy to blood diseases.

Key words: Hematopoietic stem cell, Micro environment, stem cell fate, Bone marrow Niche, factors

INTRODUCTION

Hematopoietic stem cells represent the foundational unit of the mammalian blood system, which is composed of a rare self-renewing multipotent population that exists mainly in bone marrow to produce mature blood lineages throughout an organism's entire life span describe hemopoietic stem cell as the cornerstone of the hematopoietic system, which enables stem cells to

maintain their progenitor pool through self-renewal and multilineage differentiation, abilities that separate stem cell from committed downstream progenitors and serve their essential function in hematopoietic stem cell transplantation (Pereira et al., 2024).

Since Raymond Schofield first formalized the concept of the stem cell niche in 1978, proposing

that bone marrow residency is essential for the maintenance of stem cell potency, researchers have developed a more advanced understanding of how hemopoietic stem cell identity is regulated by both intrinsic programs and the surrounding microenvironment (Yu & Scadden, 2016). This initial theoretical concept was later supported by experimental studies, including *Drosophila* germ line research, which provided evidence for the role of specialized niches in stem cell regulation (Xie & Spradling, 1998). Subsequent discoveries in the hematopoietic system demonstrated that osteoblasts act as early niche components that promote HSC maintenance through pathways such as Notch signaling (Calvi et al., 2003). Later studies using SLAM receptor mapping revealed that HSCs preferentially localize to perivascular sinusoidal regions, shifting the research focus toward vascular niche biology (Lapidot et al., 2008). Recent findings have shown that key factors such as CXCL12 and stem cell factor (SCF), which are essential for HSC maintenance, are primarily produced by leptin receptor-positive (LepR+) mesenchymal stromal cells and sinusoidal endothelial cells (Morrison & Scadden, 2014; Omatsu, 2023).

The HSC biology discipline depends on maintaining an exact distribution between three states of cellular activity which includes quiescence and self-renewal and differentiation. The steady-state HSCs are found in the G₀ phase, less than 5% percent of them actively go through the S/G2/M, a state that maintains the long term self-renewal capacity and reduces the replication associated mutagenic risk (Z. Chen et al., 2022; Ling et al., 2023). The molecular network that regulates this transition process uses intrinsic cell regulators which include cyclin-dependent kinase inhibitors p21Cip1 and p57Kip2 together with transcription factors GATA-2 and Gfi1 and epigenetic effectors DNMT3a and METTL3 to manage external signaling pathways which operate through mTOR and MEK/ERK pathways (Z. Chen et al., 2022; Ling et al., 2023; Treichel & Filippi, 2023). Leukemic stem cells in malignant conditions use signals from their niche to maintain their dormant state which protects them from chemotherapy while enabling their cancer progression. The micro-environmental factors that determine HSC fate are essential for biological processes but they also represent an urgent need for medical research (Kong et al., 2023).

Physical and Mechanical Cues

Physical cues regulate HSC quiescence, self-renewal, proliferation, and lineage commitment in conjunction with soluble growth factors and cell-cell signals. The HSC niche mechano-biology research establishes crucial insights which help scientists understand how HSCs expand outside the body and how HSCs move through transplantation and how scientists study blood cancers (Li et al., 2021; P. Zhang et al., 2019).

2.1 Extracellular Matrix (ECM) Composition and Remodeling

2.1.1 Major ECM Components and Their Roles

The bone marrow ECM consists of various collagens and glycoproteins and proteoglycans and glycosaminoglycans (GAGs) which each fulfill separate roles in adhesion and cellular communication and tissue framework construction. The BM matrix contains collagens as the most plentiful structural proteins. The matrix contains multiple collagen types which include COL1, COL3, COL4, COL5, COL6 and COL14 (Scala et al., 2025). The researchers found that HSCs cultured on collagen type I fibrils experienced reduced growth and different cell development patterns which led to their hypothesis that COL1 helps HSCs stay inactive within the endosteal niche environment (Lee-Thedieck et al., 2022). The basement membrane material collagen type IV which exists as a major component of the membrane system exists throughout endosteal and periarteriolar and sinusoidal regions to regulate PR thrombocyte development and megakaryocyte activity (Lee-Thedieck et al., 2022; Scala et al., 2025).

Fibronectin (FN) functions as a primary glycoprotein for the BM ECM since it exists as both a soluble plasma protein and an insoluble matrix protein. The study found that fibronectin functions as the strongest adhesive molecule which HSCs use to stick to material surfaces among all tested ECM ligands (Lee-Thedieck et al., 2022). The fibronectin-rich endosteum region shows higher stiffness measurements which range between 40 and 50 kPa compared to the laminin-rich perivascular region which has soft tissue properties at approximately 3 kPa demonstrating that ECM composition directly affects the biomechanical characteristics of the niche (Oudebrouckx et al., 2024).

The bioavailability of hematopoietic growth factors gets controlled by proteoglycans and glycosaminoglycans (GAGs) which include heparan sulfate proteoglycans (HSPGs) and hyaluronic acid (HA) and perlecan. Perlecan which MSCs produce maintains the BM niche connective tissue structure while preventing HSCs from attaching to it (Scala et al., 2025). Hyaluronic acid binds to CD44 receptors which are essential for HSC transplantation homing and to RHAMM receptors which together control HSC movement (Scala et al., 2025).

2.1.2 ECM Remodeling by Metalloproteinases

The collective action of MMP-2 MMP-8 MMP-9 and MMP-14 enables the process of HSC mobilization from the bone marrow to the bloodstream through their role in BM niche remodeling (Kazemi et al., 2025). The research shows that MMP-9 which both stromal cells and hematopoietic cells release can activate c-KIT receptor signaling in HSCs by cleaving membrane-bound Kit ligand to produce soluble Kit ligand. To create a balance between tissue mobilization and the maintenance of stem cell niches, TIMPs regulate MMP activities (Kazemi et al., 2025). In hematopoietic disorders, MMP and TIMP dysregulation has major pathological consequences. Myeloproliferative neoplasms and bone marrow fibrosis patients show TIMP-1 levels which increase while MMP-3 activity decreases, leading to abnormal matrix buildup and damage to HSC niche structure (Huang et al., 2022). Cytokines activate MMPs during emergency hematopoiesis to initiate rapid changes in the bone marrow matrix which allows HSCs to leave the bloodstream while the body produces more mature blood cells. The stem cell response requires MMP activity because it operates as a controllable rheostat which integrates both inflammatory signals and structural changes in the niche (Huang et al., 2020; Verma et al., 2020).

2.2 Biomechanical Properties: Stiffness and Shear Stress

According to Hasani-Sadrabadi and Li (2023) matrix stiffness functions as a primary biomechanical element which controls both cell fate determination and the aging process of tissue-specific stem cells (Hasani-Sadrabadi & Li, 2023).

2.2.1 Matrix Stiffness and Mechanosensing

The bone marrow possesses viscoelastic properties together with spatially varied stiffness characteristics. The investigation of undamaged bone marrow in pig models revealed Young's moduli values which went from 0.25 kPa to 24.7 kPa (Huang et al., 2022). The fibronectin-rich endosteal zone has a stiffness of 40 to 50 kPa which establishes its boundaries as the most rigid area within the niche. The two regions of the body establish contrasting biomechanical microenvironments through their different stiffness levels which show that the central medullary region of adipocyte composition and the laminin-rich perivascular zone both have a lower stiffness of about 3kPa (Zhang et al., 2023).

The three dimensional co culture system with BMSCs and HSCs in soft hydrogels creates a physiologically realistic environment which supports HSC preservation and lymphocyte development while reversing aging symptoms in HSCs through myeloid bias and self-renewal capacity loss restoration which enables HSCs to regain their complete ability to create different blood cell types for transplantation studies (Zhang et al., 2023). The research results show important medical applications because they demonstrate that better biomechanical design of ex vivo culture systems will lead to better results in HSC transplantation (Zhang et al., 2023).

Dynamic stiffness alterations depend on the ECM composition together with the cell population density in an area. The process of bone remodeling begins when osteoclasts activate their mineralized matrix resorption function while osteoblasts start their process of new matrix formation which results in local stiffness changes. The sympathetic nervous system signals cause osteoblasts in the bone marrow to become stiffer and undergo shape changes which control the patterns of HSC exit from the bone marrow (Katayama et al., as cited in Suzuki et al., 2016).

2.2.2 Fluid Shear Stress and PIEZO1 Mechanosensing

Wall shear stress (WSS), one of the fluid mechanical stresses that affect HSC development from embryonic stages to adult HSC fate choices, is one example of how HSC behavior is regulated. Through a 2026 Nature Aging study that became a scientific landmark, Shang, Zhao, Ying, and their research team demonstrated that PIEZO1 can detect blood-flow shear stress to trigger HSC

growth and myelopoiesis. The study showed that shear stress triggers PIEZO1 to generate ion currents and Ca^{+2} entry into human and mouse HSCs, which leads to myeloid-biased differentiation and cellular proliferation via JAM3 and CAPN2 signaling pathways (Shang et al., 2026).

The study found that continuous exposure to shear stress acts as a physiological mechanism which drives HSC aging that results from inflammation, which represents a typical aging process that leads to higher myeloid output and lower lymphoid and erythroid production capacity. Researchers tested the PIEZO1 blocker GsMTx4 (a PIEZO1 antagonist) to stop mice from developing aging symptoms which resulted from inflammation by blocking shear stress-based HSC activation, thus showing that PIEZO1 serves as an effective therapeutic target for treating hematopoietic aging (Shang et al., 2026).

2.3 Architectural Geometry of the Bone Marrow Niche

The three dimensional spatial architecture of the bone marrow ECM together with its molecular composition and mechanical properties, creates a complete system that determines HSC behavior. HSCs exist throughout the marrow cavity but they organize themselves into three specific microenvironments which include endosteal, periarteriolar, and perisinusoidal niches. These microenvironments function as distinct spatial areas which stem cells use to grow based on their particular cellular and vascular design and structural properties (Kwon et al., 2024; Morrison & Scadden, 2014).

2.3.1 The Endosteal Niche

The endosteal niche is situated between two boundaries which separate mineralized bone material from the marrow cavity area that contains trabecular bone projections (trabeculae) which form an intricate three-dimensional structure with a vast surface area. The body contains 20 to 30 percent of its nonactive HSCs together with bone surface osteoblasts while its active stem cells show a preference for blood vessel connections in the sub endosteal area (Scala et al., 2025). The histological and functional assays show that HSCs and multipotent progenitors create endosteal and sub endosteal regions which directly touch the bone surface while committed progenitors and

differentiated cells occupy central and perisinusoidal zones (Cordeiro-Spinetti et al., 2015). The two spatial divisions create separate biochemical environments which consist of endosteal compartment that contains low ROS and low metabolic activity to sustain deep quiescence and long-term self-renewal state versus sinusoidal zones which contain higher ROS and metabolic activity to support active cycling and differentiation process (Kwon et al., 2024).

2.3.2 The Periarteriolar Niche

Human stem cells achieve their most extended period of dormancy within the periarteriolar niche which exists next to the arteriolar endothelium. The arteriolar niches function to keep HSCs in a state of quiescence while maintaining reduced levels of ROS (Kwon et al., 2024). The arteriolar blood vessels create a protected zone which prevents exposure to the high fluid shear forces and oxygen levels and growth factor gradients that occur in sinusoidal regions because their endothelial walls remain mostly intact with low permeability due to the presence of smooth muscle cells. The skeletal stem cells located in periarteriolar regions show an inclination to develop into bone-forming cells which supports the maintenance of bone formation activity in this area while keeping its dormant state (Rasheed, 2022).

2.3.3 The Perisinusoidal (Vascular) Niche

The fenestrated sinusoidal vasculature establishes the perisinusoidal niche by creating a highly permeable zone which contains diverse biochemical properties that support HSCs in their active processes of cell growth and differentiation and their subsequent entry into the bloodstream. Because sinusoidal vessels have greater vascular permeability, which exposes HSCs to peripheral factors like growth factors and cytokines, HSCs in the perisinusoidal region exhibit less quiescence than those in the periarteriolar region (Rasheed, 2022).

2.3.4 Three-Dimensional Architecture and Emerging Bioengineering Models

Researchers developed advanced 3D in vitro models because conventional two-dimensional culture systems cannot reproduce the bone marrow's three dimensional spatial arrangement and cellular interactions and mechanical characteristics. The advanced 3D systems which

scientific research creates can replicate essential niche structural and mechanical signals which HSC quiescence and stemness display but 2D cultures fail to maintain (Scala et al., 2025).

The development of organ-on-chip platforms has made it possible to recreate the geometric structures of both endosteal and perivascular niches inside a microfluidic system, which includes functional vascular networks. The researchers found that their organ-on-chip system with vascularized features could replicate blood cell

development processes, which involved sustaining and converting CD34⁺ HSPCs and neutrophils as they moved through the microvascular system thus creating an authentic reproduction of bone marrow activities in the lab. The platforms now possess advanced resolution capabilities, which enable researchers to investigate how drug treatments, growth factor applications, and disease-related disruptions specifically affect different niche types (Glaser et al., 2022).

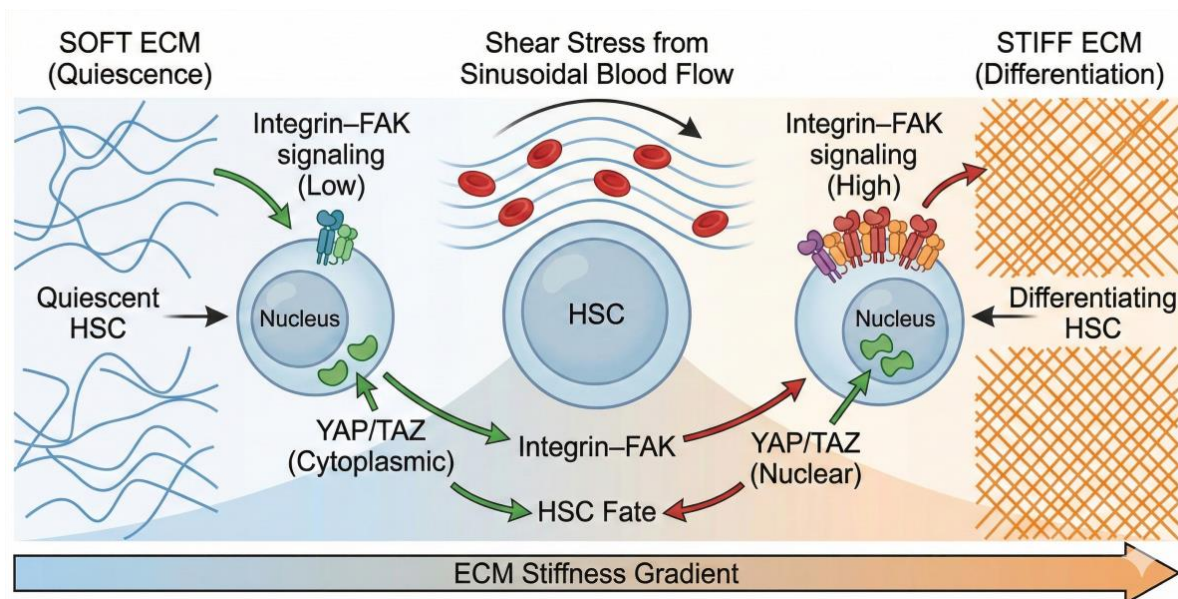


Fig 01: Physical and mechanical regulation of HSC fate

3. Spatial and Functional Heterogeneity of HSC Niches

The spatial and functional heterogeneity of hematopoietic stem cell (HSC) niches is given by discrete microenvironment of the bone marrow that coordinates the HSC fate decisions. The endosteal niche lies adjacent to the bone surface and is defined by a rather hypoxic environment and support of HSC quiescence and self-renewal by interactions with osteoblasts and secretion of regulatory factors, whereas the perivascular niche is related to sinusoidally protruding endothelium and promotes HSC proliferation and differentiation (Busch et al., 2024). In the perivascular compartment, the quiescent HSCs are preferentially associated with the arteriolar niches, and the more proliferative HSC populations tend to be found in the sinusoidal niches, which consequently results in the functional differences between the vascular subtypes (Shi et al., 2023). Localization patterns also depend on the status of

the activity of HSCs, dormant HSCs are known to be located in hypoxic endosteal areas, thus maintaining a long term self-renewal ability, but activated HSCs are located more related to vascular niches, where they participate in proliferation and differentiation (Shi et al., 2023). Additionally, regional bone marrow oxygen gradients result in zoning of the microenvironment for controlling the metabolism and differentiation of the HSCs, as reduced oxygen tension in the endosteal niche results in stemness and increased oxygen tension in the bone marrow of the sinusoids results in differentiation (Busch et al., 2024). These regional variations are also modulated by biochemical factors such as CXCL8 and protein kinase C, which are involved in controlling the occupancy of niches and competition between HSCs, thus indicating a complex relationship between spatial position and biochemical regulation of haematopoiesis (Binder et al., 2023).

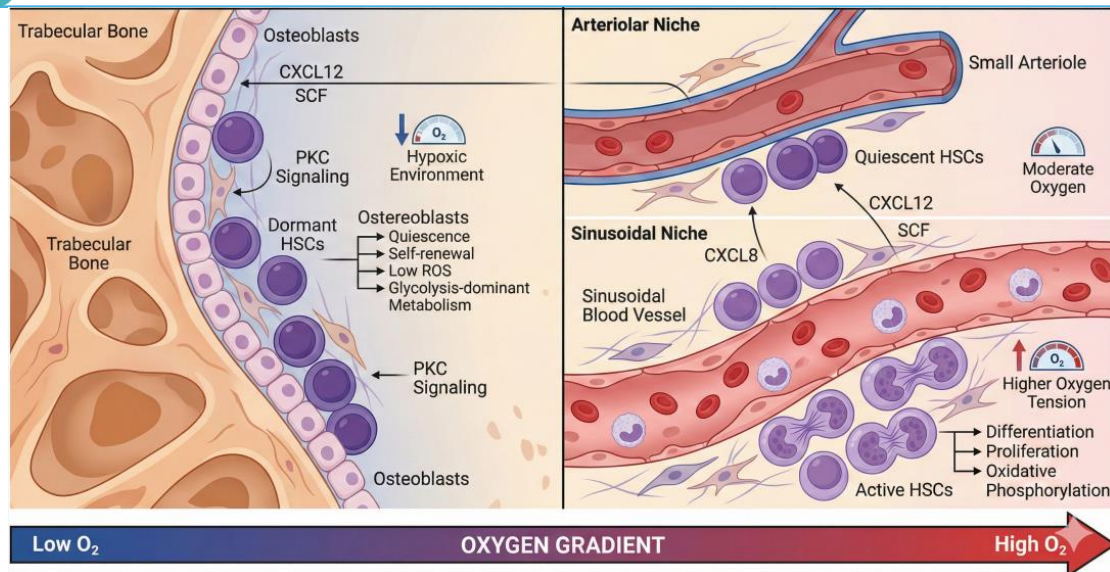


Fig 02: A Compartmental cross sectional diagram of bone marrow showing Endosteal Niche (left side) and perivascular niche (right side)

4. Chemical and Soluble regulatory factors

The hematopoietic microenvironment contains chemicals and soluble factors and plays an essential role in maintaining hematopoietic stem cells (HSCs) because these factors mediate cellular localization, self-renewal, proliferation, and differentiation. Consequences of these constituents include cytokines, chemokines, growth factors, and adhesion molecules which promote HSC adherence to their niche and allow them to be responsive to extrinsic signals, maintaining a stable stem-cell reservoir. Mesenchymal stromal cells and differentiating hematopoietic progeny release soluble mediators that form a dynamic signalling network that controls HSC fate choices; combinations of cytokines, including TGF- β 1 have been shown to enhance HSC maintenance in engineered niches (Gilchrist & Harley, 2020). Moreover, the antagonistic influence of the extrinsic factors on the HSC maintenance is the renal protein Klotho, as well as inorganic phosphate, which also adjusts metabolic and signalling pathways in the bone-marrow niche (Du et al., 2022). Purinergic signalling and complement cascade are also involved in this regulation as they are also known to regulate immune responses and intracellular signalling in stressed HSCs (Franczak et al., 2025).

4.1 Role of Cytokines and Chemokines (SDF-1/CXCR4 Axis)

Cytokines and chemokines play an important role in the maintenance, migration and developmental

choices of HSC. The interplay between the SDF1 (CXCL12)/CXCR4 is one of the primary signalling pathways of chemokines that keep the HSCs in the bone-marrow niche by promoting the adhesion to stromal cells and maintaining quiescence. CXCL12 secreted by mesenchymal stem and progenitor cells (MSPCs) and endothelial cells is used to draw HSCs with CXCR4 expression, which then allows them to localize to favorable niches and access vital growth factors (Miao et al., 2020). The axis also plays a role in immune cell development and memory preservation because it guides the progenitors, as well as the differentiated immune cells, to the bone marrow (Miao et al., 2020). This signalling failure disrupts the retention and functionality of HSC highlighting its core role in haematopoiesis (Miao et al., 2020).

4.2 Growth Factors Signalling (SCF, TPO and TGF- β)

The Stem Cell Factor (SCF), Thrombopoietin (TPO), and Transforming Growth Factor-beta (TGF- β) are growth factors that play a vital role in regulating the self-renewal of HSCs, their survival, quiescence, and differentiation. SCF interacts with the c-Kit receptor on the HSCs to enhance survival and proliferation; it is released by bone-marrow stromal cells such as adipose tissue-derived cells to regulate the metabolism of haematopoiesis (Lee et al., 2020; Z. Zhang et al., 2019). TPO maintains the quiescence and self-renewal of HSC via its receptor MPL, which maintains the stem-cell pool (Lee et

al., 2020). TGF- β triggers quiescence where it blocks proliferation, but at the same time, it acts on lineage commitment depending on the context (Lee et al., 2020).

4.3 Metabolic Programming of HSCs

HSCs mainly depend on anaerobic glycolysis because they inhabit hypoxic bone-marrow niches; such a metabolic profile suppresses the production of reactive oxygen species and stemness. In the process of differentiation, metabolic changes to oxidative phosphorylation are established, which is the ability to satisfy increased energy requirements (Oburoglu et al., 2016). Mitochondrial quality control in HSCs is controlled by mitochondrial fission and fusion, and proper dynamics must be maintained to ensure the functionality of the stem cells through balancing energy generation and reactive oxygen species (Oburoglu et al., 2016). The NAD⁺ dependent sirtuin family contributes to the longevity of HSCs by acting via the epigenetic regulation and metabolic control processes that regulate DNA repair, oxidative stress response, and mitochondrial activities (Oburoglu et al., 2016). Under homeostatic conditions or metabolic stress, fatty acid oxidation is important to sustain asymmetric division of HSCs and self-renewal capacity and AMPK is an energy sensor, which triggers catabolic pathways resulting in quiescence when nutrients are scarce or during stress (Oburoglu et al., 2016; Z. Zhang et al., 2019).

5. Cellular Components of the Microenvironment

The cellular components of the hematopoietic microenvironment are a complicated heterogeneous network that controls the maintenance, proliferation, and variation of the hematopoietic stem cells (HSCs).

5.1 Mesenchymal Stromal Cells and Osteoblast

Mesenchymal stromal cells (MSCs) are the crucial elements of the hematopoietic microenvironment as they offer architectural support, and regulatory cues in the HSC maintenance. MSCs produce cytokines, chemokines and growth factors, which regulate HSC quiescence, self-renewal and differentiation by paracrine signaling in addition to direct cell contact. They give rise to other niche cell types as well including osteoblasts which lining up the endosteal bone perimeter play a role in regulating the HSC by releasing factors that induce

stem cell quiescence and maintenance in the niche (Busch et al., 2024).

5.2 Vascular and Endothelial Niche Interaction

The endothelial cells lining the sinuously-shaped blood vessels make up the vascular niche in the bone marrow, with perivascular stromal cells. This niche enhances HSCs proliferation and differentiation as opposed to osteoblastic niche which supports quiescence. Endothelial cells secrete factors that are essential to the HSCs homeostasis and engage with the HSCs through adhesion factors to control their localization and functionality (Comazzetto et al., 2021; Tikhonova et al., 2019). Transcriptomic single cell studies demonstrate that there are heterogeneities in vascular niche cells and changes that occur dynamically in response to stress conditions and affect HSC lineage commitment (Tikhonova et al., 2019). There are also perivascular leptin receptor positive stromal cells that produce the necessary growth factors to sustain HSCs and progenitors (Comazzetto et al., 2021).

5.3 Inflammatory and Immune Cell Signals

The bone marrow microenvironment provides an inflammatory signal that regulates HSC behavioral changes in response to stress or disease conditions by changing cytokine-based responses and cellular communications. Macrophages are the immune cells involved in niche regulation through the release of inflammatory mediators that either induce HSC activation or their quiescence depending on the circumstances (Medyouf, 2017). The remodelling of the niche as a result of chronic inflammation or malignancy frequently interferes with the normal haematopoiesis by altering cellular composition and signalling networks to promote the survival of malignant stem-cells at the expense of normal HSC functions (Medyouf, 2017).

6. Key Molecular Signaling Pathways

6.1 Notch and Wnt Signaling in Self-Renewal

Notch signaling happens due to HSC's direct cell to cell communication with neighboring stromal or endothelial cells presenting Jagged or Delta like ligands. When one of these receptors is triggered, an intracellular domain of Notch is cleaved which initiates a gene program that maintains stemness and also limits premature lineage commitment. Current models suggest that the activated but functionally quiescent state of Notch is predominant in adult HSCs and protects from the

exhaustion of regenerative stress (Siebel & Lendahl, 2017).

Table 01: Microenvironmental Factors and Their Functional Effects on HSC Fate

Factor Category	Specific Factor	Primary Source Cell(s)	Mechanism/ Signaling Pathway	Functional Effect on HSC	References
Soluble Factors	SCF (Stem Cell Factor)	MSCs/ Adipose-derived cells	c-Kit receptor activation	The survival, self-renewal and proliferation	Lee et al., 2020; Z. Zhang et al., 2019
	CXCL12 (SDF-1)	MSCs/ CAR cells/ Endothelial cells	CXCR4 signaling axis	Stasis in niche, homing and quiescence	Miao et al., 2020; Morrison & Scadden, 2014
	TPO (Thrombopoietin)	Liver/ Bone Marrow Stroma	MPL receptor binding	Stem cell pool and quiescence	Lee et al., 2020
	TGF- β	Megakaryocytes/ Osteoblasts	SMAD pathway	Quiescence induction; proliferation inhibitor	Lee et al., 2020
ECM Components	Collagen Type I	Osteoblasts / Stromal cells	Signaling of high-stiffness matrices.	Inhibits HSCs activation; attaches HSCs to endosteum	Lee-Thedieck et al., 2022; Scala et al., 2025
	Fibronectin	MSCs/ Plasma	Integrin receptors $\alpha 5\beta 1$, $\alpha 4\beta 1$	Altering motility and cell division, as well as strong adhesion	Lee-Thedieck et al., 2022; Oudebrouckx et al., 2024
	Osteopontin (OPN)	Osteoblasts	Integrin $\alpha 9\beta 1$ binding	Minimum regulator; constrains the size of the HSC pool	Lee-Thedieck et al., 2022
	Hyaluronic Acid	ECM / MSCs	CD44 and RHAMM receptors	Controls the migration and homing of post-transplant	Scala et al., 2025
Mechanical Cues	Matrix Stiffness	Endosteal Niche (High stiffness)	YAP/TAZ signaling/ PIEZO	Regulates aging; soft niches maintenance	Hasani-Sadrabadi & Li, 2023; Zhang et al., 2023
	Shear Stress	Blood flow (Sinusoids)	PIEZO1/ Ca^{+2} entry	Stimulated proliferation and differentiation to myeloid	Shang et al., 2026; Li et al., 2021
Architectural/ Metabolic	Hypoxia (Low O_2)	Periarteriolar Niche	Anaerobic glycolysis	Inhibits the formation of ROS; prevents stemness	Oburoglu et al., 2016
	MMPs (e.g., MMP-9)	Stromal/ Hematopoietic cells	Cleavage of membrane bound SCF	Induces release of HSC in the blood	Kazemi et al., 2025

The effect of Notch signaling however seems to be dependent on context. The over activation or sustained activation can result in impaired lineage production or add to the development of leukemogenesis, and the lack of such signaling leads to attenuation of self renewal. The latter displays the significance of balanced interactions between receptors and ligands in the niche microarchitecture (Pandey et al., 2024).

Wnt signaling, another crucial component of HSC regulation, is an example of such a parallel. By stabilizing 2-catenin, canonical Wnt signaling maintains transcriptional programs linked to stem cell proliferation. Experimental evidence has demonstrated that while hyperactivation destabilizes the state of differentiation, moderate β -catenin activation enhances long-term repopulating capacity (Zanetti et al., 2021).

This environment is made more heterogeneous with non-canonical Wnt signaling. Wnt pathways. An example is that Wnt5a signaling has been involved in the regulation of HSC quiescence and the oxidative stress full of anti-stress measures, which safeguard stem cell integrity during aging and inflammatory stress (Sarabia-Sánchez & Robles-Flores, 2024).

Notably, the two pathways, Notch and Wnt are cross-talked to permit dynamic responsiveness to the systemic requirements like infection or hematopoietic damages. Stromal cells regulate the occurrence of ligands in accordance with the presence of inflammatory mediators, thus changing the strength of pathways and reorganizing HSC fate choices (Morrison & Scadden, 2014).

6.2 Epigenetic Modifications Driven by Niche Cues

The long-term fate decision in hematopoietic stem cells (HSCs) is categorized by epigenetics, even though the fast transcriptional responses start with signaling pathways. The molecular memory systems that encode environmental factors in HSCs are DNA methylation, chromatin remodeling, and histone modifications (Wang et al., 2022). DNMT3A, TET2, and ASXL1 are examples of epigenetic regulators that are controlled by inflammatory cytokines and metabolic alterations brought on by niches. Considering that the accumulation of mutations in these regulators during the aging process is frequently seen in clonal hematopoiesis cases, there is a correlation with altered chromatin landscapes and microenvironmental stress (Bolton et al., 2020).

Recent advances in the fields of transcriptomic and epigenomic profiling research have suggested that chronic inflammatory cues induce alterations in the enhancer landscape of HSCs, resulting in myeloid-biased differentiation and reduced lymphoid output (Yang et al., 2023). Metastatic conditions in the niche also affect methylation. Hypoxia-stimulating factors and modifications in mitochondrial metabolism that facilitate the maintenance of quiescence or activation statuses under various environmental conditions control the patterns of histone acetylation (Morganti et al., 2022).

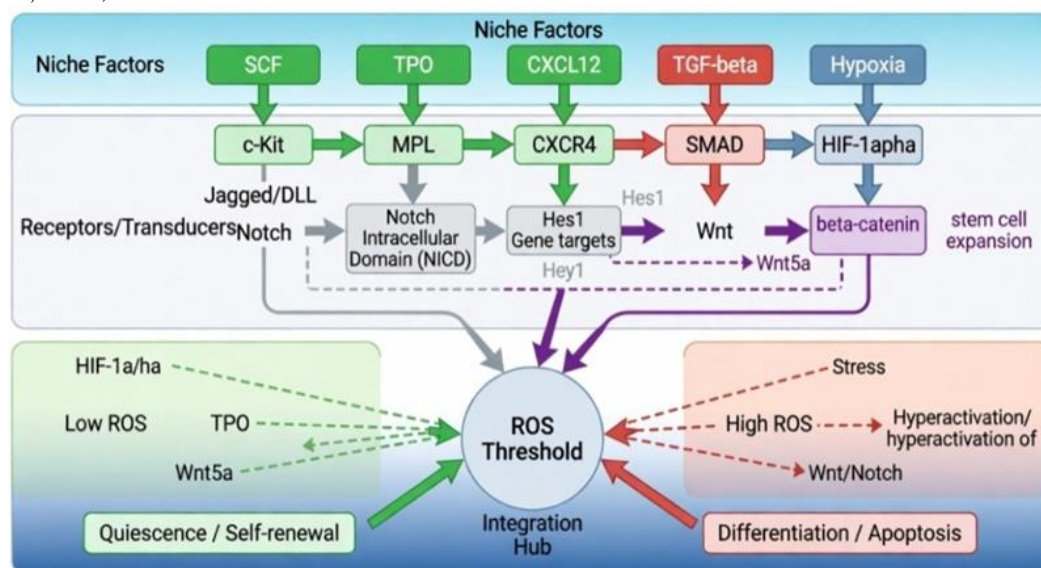


Fig 03: Key Molecular Signaling Pathway

7. Pathological Alterations in the Microenvironment

7.1 The Aging Niche (Inflammaging)

The structural and molecular makeup of the bone marrow niche changes significantly with age. Supportive factors like stem cell factor and CXCL12 are produced less frequently as a result of increased adipogenesis, decreased osteoblastic activity and vasculature remodelling (Kandarakov et al., 2022). Inflammaging or low grade chronic inflammation is a defining characteristic of the aged niche. Elevated levels of TNF- α interferons and IL6 stimulate HSCs to initiate stress responses that lead to functional loss and proliferative stress (Ergen & Goodell, 2010).

The experimental models of transplantation show that old niches can transfer transcriptional aging signatures to young HSCs, and thus the strong effect of extrinsic factors (Lévesque et al., 2021).

7.2 The Leukemic Niche: How Malignancy Hijacks the Environment

Leukaemia related LSCs exploit and modify the bone marrow's microenvironment to increase their chances of survival. To prevent normal haematopoiesis, malignant cells alter the expression of adhesion molecules, cytokines, and extracellular matrix (Fallati et al., 2022). The breakdown of Notch signalling pathways is common in leukemic niches. Aberrant activation promotes self-renewal in LSCs and also helps to prevent the apoptosis of the cells caused by chemotherapy (Viñado et al., 2022). Leukemic remodelling also promotes immune evasion. Cytotoxic T cells are suppressed and macrophages encouraged to promote tumor-supportive phenotypes which helps the disease to persist (Barachini et al., 2025).

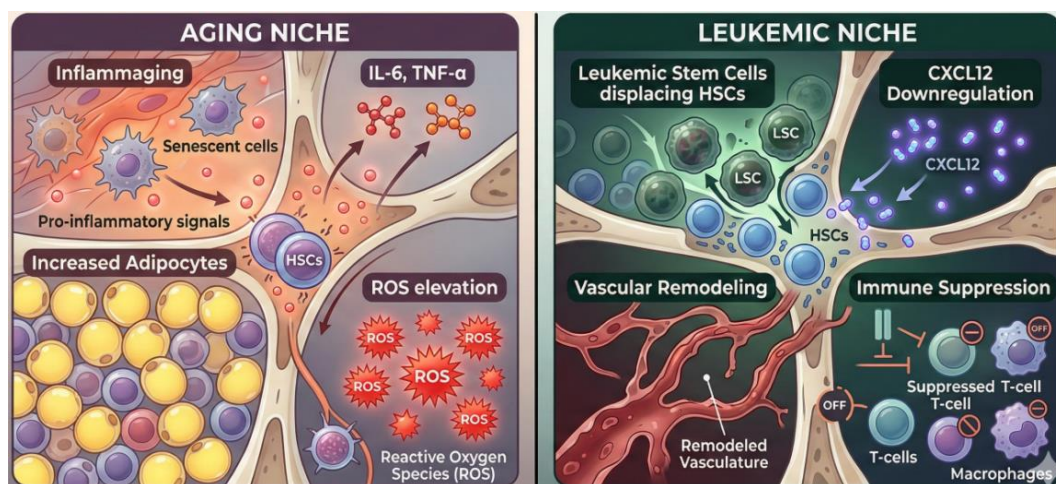


Figure 04: Contrasting Aging v/s Leukemic Niche

8. Clinical and Therapeutic Applications

The clarification of the biology of the hematopoietic stem cell (HSC) niche has spurred new research directions that can improve the therapy of hematologic disorders and the field of regenerative medicine. Modulation of micro-environmental signals and overcoming chemo-resistance have led to researchers getting better results in bone marrow transplantation.

8.1 Bioengineering Synthetic Niches for Ex Vivo Expansion:

The greatest challenge facing Hematopoietic stem cell transplantation (HSCT) is the limited number of donor cells. To overcome this problem, researchers have suggested a three dimensional bio-

mimetic scaffold, which is a fabrication of physical bone marrow properties. These artificial niches make use of microfluidic organ-on-chip technology to allow an out-of-body regulation of HSC growth whilst maintaining the self-renewal ability of the stem cells (Hong et al., 2024).

8.2 Niche-Targeting Therapies in Hematology:

The niche provides the leukemic cells with a haven where they avoid chemotherapeutic destruction by patients with acute myeloid leukemia (AML) and other hematologic malignancies. The therapeutic approaches are expected to interfere with the communication between the malignant cells and the bone marrow stroma targeting the CXCL12/CXCR4 axis (Mendez-Ferrer et al.,

2024). The activation of these cells out of their protective microenvironment increases their vulnerability to all-inclusive treatment procedures (Y. Chen et al., 2022; Stelmach & Trumpp, 2023).

8.3 Enhancing Engraftment and Homing:

Scientists developed priming agents through their research on how chemical gradients function

within the niche. The simultaneous co culture of the small molecules and enzymes allows marrow pre-conditioning of recipients thus enhancing homing efficiency of transplanted HSCs to their target niche and successful engraftment (Huang & Broxmeyer, 2019; Ratajczak & Suszynska, 2016).

Translational Pipeline for HSC Niche Therapeutics

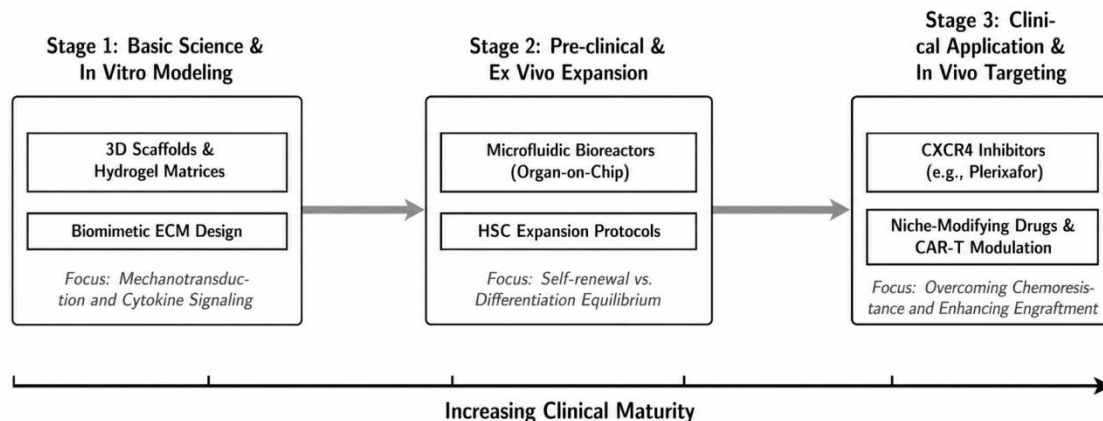


Fig. 05. Bioengineered and Therapeutic Targeting Strategies

9. Future Perspectives and Directions

The future path of Hematopoietic Stem Cells depends on their interactions with all elements present in their surrounding environment. Blood production happens through the coordinated action of physical forces and soluble factors together with neighboring cells which establish a network of regulatory mechanisms. The review demonstrates that no individual factor exists as an independent entity because the combination of physical mechanical forces (stiffness and shear stress) with chemical gradients (hypoxia and cytokines) and cellular interactions (MSCs, vascular, and neural cells) creates the mechanism which sustains the equilibrium between quiescence and self-renewal and differentiation. Despite the current significant progress in the identification of niche components, there are still difficulties in the translation of laboratory findings into clinical practice. The malignant niche paradigm explains how leukemic cells hijack regulatory cues leading to the creation of the protective microenvironments, which suppress the traditional therapies (Wei & Frenette, 2018; P. Zhang et al., 2019).

The current situation has seen better results but there continue to be substantial challenges. Future

research should prioritize following things: The latest imaging technologies can be used to analyze HSC communication patterns when they engage with other cells in their native microenvironment (Bandyopadhyay et al., 2024). The researchers need to develop methods which will restore youthfulness to elderly bone marrow microenvironments because this approach will decrease the risk of age-related blood cancers developing (Hofmann & Kokkaliaris, 2024). The scientists develop patient specific cellular models to substitute the traditional animal tests and thus create customized testing systems (Kandarakov et al., 2022; Man et al., 2021).

Conclusion

The fate of hematopoietic stem cells (HSCs) is not determined independently but it is extraordinarily controlled by the dynamic microenvironment of the bone marrow niche. As discussed in this review, hematopoiesis relies on a very robust network of physical forces, including matrix stiffness and shear stress, and is fitted together with chemical gradients and cellular interactions. Regardless of whether it is the hypoxic endosteal zone or the active perivascular space, HSC fate choices, such as quiescence, self-renewal and differentiation, are continuously adjusted by such

microenvironmental signals and their corresponding molecular pathways, such as the Notch and Wnt signaling, respectively. Comprehending these complicated interactions has far reaching clinical consequences. Instability of the niche is a major contributor to pathological conditions that can cause a benign environment into an inflammaging environment within the geriatric or a protective home to malignant stem cells that occur in leukemia. The decoding of the native niche has enabled the researchers to bridge the gap between the basic science and the advanced therapeutics effectively. A significant innovation in translational medicine has been the development of bioengineered 3-D scaffolds, ex vivo organ-on-a-chip bioreactors and targeted pharmacological therapies including CXCR4 inhibitors.

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