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REVIEW ARTICLE

Stem cell biology

Hematopoietic stem and progenitor cell signaling in the niche

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Abstract

Hematopoietic stem and progenitor cells (HSPCs) are responsible for lifelong maintenance of hematopoiesis through self-renewal and differentiation into mature blood cell lineages. Traditional models hold that HSPCs guard homeostatic function and adapt to regenerative demand by integrating cell-autonomous, intrinsic programs with extrinsic cues from the niche. Despite the biologic significance, little is known about the active roles HSPCs partake in reciprocally shaping the function of their microenvironment. Here, we review evidence of signals emerging from HSPCs through secreted autocrine or paracrine factors, including extracellular vesicles, and via direct contact within the niche. We also discuss the functional impact of direct cellular interactions between hematopoietic elements on niche occupancy in the context of leukemic infiltration. The aggregate data support a model whereby HSPCs are active participants in the dynamic adaptation of the stem cell niche unit during development and homeostasis, and under inflammatory stress, malignancy, or transplantation.

Introduction

A heterogeneous population of hematopoietic stem and progenitor cells (HSPCs) sustain lifelong organ function through the ability to self-renew and differentiate into mature cell lineages. During adult life, operationally-defined, highly specialized core units, termed niches, support HSPC residence and maintain cells in a predominantly quiescent state to prevent exhaustion [1, 2]. In response to systemic demand or injury, a small number of long-lived stem cells emerge to undergo asymmetric cell division, allowing simultaneous self-renewal and hematopoietic differentiation [3]. A central tenet of HSPC biology is that overall function is governed by integrating cell-intrinsic programs with extrinsic cues. These unique capabilities rely upon extensive and tightly controlled cell-to-cell communication between constituent niche components and HSPCs.

A growing body of research, predominantly in murine models, has examined the role of individual elements in the bone marrow (BM) niche in regulating HSPCs. Various non-hematopoietic cells, including BM fibroblasts, endothelial cells, and osteoblasts provide juxtacrine and paracrine signals received by HSPCs, including hematopoietic growth factors, chemokines, cytokines, morphogens, and adhesion molecules [4–6]. For example, osteoblast-derived factors such as angiopoietin-1 (ANGPT1) and thrombopoietin (TPO) guard HSPC quiescence by binding the respective cognate TIE2 and MPL receptors expressed on stem cells [7, 8]. Similarly, C-X-C Motif Chemokine Receptor 4 (CXCR4) signaling via contact with perivascular C-X-C motif chemokine 12 (CXCL12)-abundant reticular (CAR) cells is critical to HSPC pool maintenance and expansion [9].

Adding to the apparent complexity of the niche, differentiated progeny such as megakaryocytes and macrophages influence HSPC quiescence, proliferation, or migration. For example, megakaryocyte secretion of CXCL4 directly influences HSPC quiescence through promotion of adhesion to nearby stromal cells and interference with HSPC interleukin (IL)-8 signaling [10]. BM macrophages are also critical for production of HSPC-trophic cytokines and maintenance of HSPCs in the niche [11]. Similar crosstalk is likely to exist between stem cells and multipotent progenitors.

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Table 1 Key findings of HSPC-initiated crosstalk within the bone marrow niche.

HSPC-interacting cells	Crosstalk modality	Mechanism	Observed effect	Reference
MPPs, myeloblasts, erythroblasts, megakaryoblasts, endothelial cells	Autocrine and paracrine signaling	Secreted factors	HSPC survival and proliferation; hematopoietic precursor chemoattraction; endothelial cell activation	Majka et al. *Blood*; 2001. [13]
HSPCs	Autocrine signaling	VEGF internal autocrine loop	HSPC survival and repopulation	Gerber et al. *Nature*; 2002. [19]
Osteoblasts	HSPC to niche signaling	Cell contact-mediated transfer of signaling membrane microdomains	Osteoblast SMAD signaling downregulation; augmented CXCL12 secretion	Gillette et al. *Nat Cell Biol*; 2009. [43]
Endothelial cells	HSPC to niche signaling	Secreted ANGPT1	Increased vascular integrity	Zhou et al. *Elife*; 2015. [49]
MSCs	HSPC to niche signaling	Secreted BMP-2 and BMP-6	Osteoblast differentiation	Jung et al. *Stem Cells*; 2008. [44]
BMSCs	HSPC to niche signaling	Connexin-43 dependent gap junctions	ROS transfer; HSPC survival and proliferation	Taniguchi Ishikawa et al. *Proc Natl Acad Sci USA*; 2012. [48]
HSPCs	Cell-cell competition	Selective growth advantage	p53-mediated cellular fitness	Bondar et al. *Cell Stem* Cell; 2010. [55]
LSCs	Cell-cell competition	Physical growth competition	Dose-dependent spatial occupancy	Boyd et al. *J Exp Med*; 2014. [65]
Leukemia cells	Cell-cell competition	Physical growth competition	Dose-dependent spatial occupancy	Glait-Santar et al. *Stem Cells*; 2015. [68]
HSPCs, leukemia cells	EV crosstalk	VPS33b-dependent EVs	HSPC and LSC quiescence, self-renewal, repopulation	Gu et al. *J Clin Invest*; 2016. [78]
Endothelial cells	EV crosstalk	Secreted EVs	Angiogenesis	Sahoo et al. *Circ Res*; 2011. [80]

HSPCs hematopoietic stem and progenitor cells, *MPPs* multipotent progenitors, *MSCs* mesenchymal stem cells, *BMSCs* bone marrow stromal cells, *LSCs* leukemia stem cells, *ROS* reactive oxygen species.

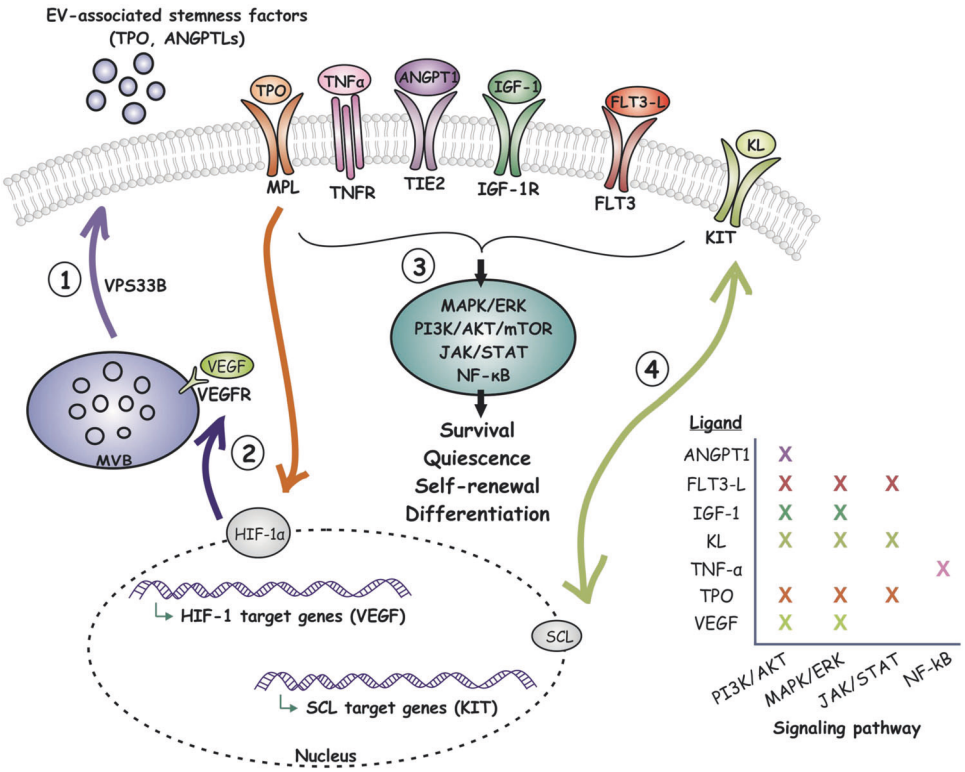

Fig. 1 Autocrine signals provide multiple mechanisms of governing hematopoietic stem and progenitor cell function. Numerous ligand and receptor interactions participate in driving HSPC behavior. (1) Self-signaling events occur in part via VPS33B-dependent extracellular vesicle (EV) secretion of factors including thrombopoietin (TPO), angiopoietin-like protein (ANGPTL)-2 and ANGPTL3. (2) Positive feedback loops enhance cooperative signals, such as TPO and hypoxia-inducible factor 1 alpha (HIF-1α)-driven transcription of vascular endothelial growth factor (VEGF; see main text). (3) Autocrine ligand-receptor signals converge on key common transduction pathways to regulate a balance between HSPC survival, quiescence, proliferation, and differentiation. (4) Key transcription factors additionally regulate cell autonomous responses. For example, binding of Kit ligand (KL) to its receptor, KIT, results in activation of the transcription factor SCL, which in turns upregulates KIT and enhances HSPC sensitivity to secreted KL. MVB multivesicular body, TNFα tumor necrosis factor alpha, TNFR TNF receptor, ANGPT1 angiopoietin-1, IGF-1 insulin-like growth factor-1, IGF-1R IGF-1 receptor, FLT3(-L) fms-related receptor tyrosine kinase 3 (ligand), VEGFR VEGF receptor, MAPK mitogen-activated protein kinase, PI3K phosphatidylinositol-3-kinase, mTOR mammalian target of rapamycin, JAK/STAT Janus kinase/signal transducers and activators of transcription, NF-κB Nuclear factor-κB.

While the prevailing model of HSPCs as passive targets of exocrine signals has been thoroughly vetted, it is conceptually limiting. Evidence continues to accrue in support of a more active role for HSPCs in shaping niche function and maintaining their own multipotency and self-renewal capacities. These observations span both murine and human systems, where immunophenotypic and functional differences exist [12], and across heterogeneous subpopulations of HSPCs with divergent lineage commitment at various stages of maturity. In acknowledging the prevailing uncertainty regarding the immunophenotypic identification of long-term stem cells in human, and the fluid boundaries of lineage commitment in mice, we therefore rely on the "HSPC" designation throughout. Here we review the secreted signals including extracellular vesicles (EVs) employed by HSPCs to regulate their own function directly and indirectly through other cells in a dynamic and functionally adaptive microenvironment (Table 1). This proposed, more inclusive view of reciprocal HSPC-niche crosstalk readily accommodates seminal observations of physiologic cell-cell competition, niche-occupancy, and clonal extinction in addition to providing insight into leukemia cell signaling.

Autocrine secretory signals contribute to HSPC self-renewal and expansion

HSPCs have long been known to play active roles in self-maintenance through autocrine secretory activity. For example, highly enriched human CD34-positive BM-derived cells secrete self-renewal regulatory factors including Kit ligand, TPO, and ANGPT1 that bind to their respective KIT, MPL, and TIE2 receptors on HSPCs (Fig. 1) [13–15]. HSPC-derived insulin-like growth factor-1 (IGF-1) may also contribute to auto-protection from

apoptotic cell death [14]. Human CD34-positive cells additionally express TNF receptors and CD95 (FAS) while secreting detectable levels of TNF-α and Fas ligand (Fas-L) [13, 14, 16]. Interestingly, soluble Fas-L may stimulate HSPC proliferation, while the relative insensitivity of human HSPCs to FAS-mediated apoptosis may in part be regulated by modulating expression of FLICE inhibitory protein (FLIP) [17]. Emerging evidence also implicates the possibility of autocrine secretion of ATP and its metabolite adenosine in regulating the mobilization of HSPCs through purinergic activation of the Nlrp3 inflammasome [18].

In a mechanism distinct from its well described role in angiogenesis, vascular endothelial growth factor (VEGF) also promotes HSPC survival and repopulation via an internal autocrine loop (Fig. 1) [19]. Mechanistically unique, VEGF-induced HSPC renewal is not inhibited by extracellularly-acting inhibitors, but rather necessitates the interaction of an internally acting ligand with its receptors VEGFR1 and VEGFR2, possibly at an endosomal membrane. These signaling events may be further amplified by HSPC production of secreted TPO, which stimulates glycolysis through interaction with its receptor MPL on the cell surface, generating increased reactive oxygen species with subsequent activation of the VEGF transcription factor, hypoxia-inducible factor 1alpha (HIF-1α) (Fig. 1) [20]. In a similar pre-secretory mechanism, IL-3 may drive autocrine growth by interaction with its receptor in HSPCs prior to surface display [21].

Additional autocrine factors likely involved in various HSPC functions include hepatocyte growth factor (HGF), RANTES (CCL5), IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF), angiopoietin-2 (ANGPT2), IL-8, BMP6, SPP1, and TNFSF10 [22, 23]. Several non-overlapping discovery approaches including gene expression profiling and computational modeling suggest that more putative autocrine regulatory loops may exist. For example, HSPCs express dual receptor and ligand gene products, including FGF/FGFR, PDGF/PDGFR, IL-4/IL-4R, Wnt/Frz, Dll1/Notch1, and Jag2/Notch1 [24].

Autocrine TGF-β signals

As critical developmental morphogens and HSPC quiescence factors, secreted transforming growth factor (TGF)-β1 and TGF-β2 play pleiotropic roles in regulating HSPC proliferation. Several early studies suggest a role for TGF-β1 in negative regulation of cell cycling in HSPCs in vitro [25]. Experimental blockade with anti-TGF-β1 antibody significantly increased in vitro HSPC cycling and accelerated subsequent HSPC engraftment. In contrast, a biphasic dose response of TGF-β2 on HSPC proliferation may exist, such that low concentrations of TGF-β2 yield a stimulatory effect on cell expansion (perhaps mirroring in vivo phenomena) while higher concentrations are inhibitory [26]. Although not well understood, autocrine and paracrine signaling mechanisms possibly differ with respect to TGF-β functions [27]. For instance, in vivo HSPCs from conditional Tgf-β type I receptor gene knockout mice were found to exhibit normal cell cycling in the context of an otherwise intact BM niche, and retained a similar ability to repopulate recipient mice following BM transplantation [28]. Moreover, autocrine activity by distinct HSPC subtypes may respond differently to TGF-β, where myeloid-biased HSPCs undergo growth stimulation, yet lymphoid-biased HSPCs are growth inhibited [29]. Conceptually, dynamic receptor expression, alternative splice variants, surface shedding, degradation, and endosomal receptor reuptake provide a system for continuous tuning that can account for highly context dependent effects of secreted TGF-β on HSPCs, as evident in other tissues [30, 31].

Shared cellular signaling nodes

Downstream of canonical cell surface ligand-receptor binding, many autocrine events converge on shared core pathways including phosphatidylinositol-3-kinase (PI3K)/AKT, mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK)/ERK, and Janus kinase/signal transducers and activators of transcription (JAK/STAT) to balance cell survival, renewal, and quiescence (Fig. 1). Several key transcription factors modulated by these transduction pathways regulate HSPC quiescence. For example, the proto-oncogene PBX1 positively regulates HSPC quiescence by sensitizing cells to TGF-β signaling [32]. Loss of transcription factors including GATA-2 and STAT5 downstream of ERK and JAK/STAT signaling respectively has been demonstrated to lead to decreased HSPC quiescence [33, 34]. SCL/TAL1, a pivotal hematopoietic transcriptional regulator, establishes a positive feedback loop with KIT to control quiescence in adult HSPCs (Fig. 1) [35]. In embryonic HSPCs, SCL is believed to alternatively contribute to cellular proliferation through induction of mTOR-driven protein synthesis [36]. Finally, activation of MYC downstream of ERK signaling coincides with downregulation of adhesion factors on HSPCs, enabling release of cells from their differentiation-suppressive niche [37].

Altogether, secretory activity is a fundamental HSPC property that enables critical autocrine signals to balance core functions, such as quiescence, proliferation, and differentiation in support of long-term pool integrity. HSPCs equipped for self-communication also allow for the possibility of neighbor crosstalk. In the context of bystander cells in the niche sharing similar ligand-receptor interactions as HSPCs, relative receptor affinity and surface density may become key mechanisms to segregate autocrine from

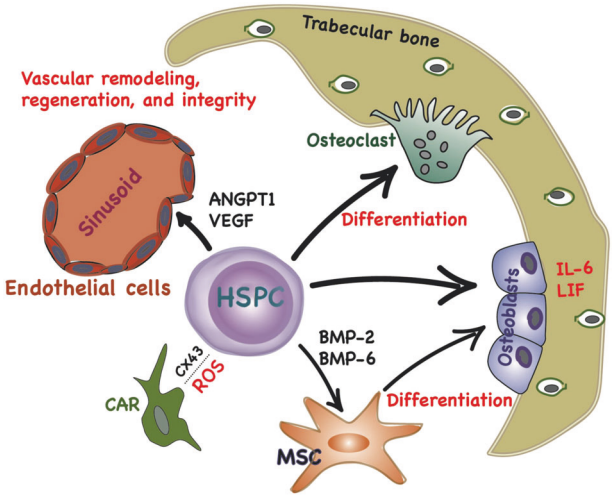

Fig. 2 Hematopoietic stem and progenitor cells actively modulate cells in their bone marrow niche. While numerous studies have focused on the impact of bone marrow (BM) niche cells on HSPC function, little is known about the reciprocol activities driven by HSPCs in modulating a permissive microenvironment. It is clear that HSPCs trigger endothelial remodeling and proliferation through secreted factors such as vascular endothelial growth factor (VEGF) and angiopoietin-1 (ANGPT1). Under stress, ANGPT1 is required to regenerate intact BM vasculature. Bone turnover and hematopoiesis are also closely linked. Through unknown secreted factors, HSPCs drive osteoblast secretion of IL-6, which among many functions, promotes osteoclastogenesis from precursor hematopoietic cells and subsequent bone resorption. Physiologic bone turnover is critical for HSPC engraftment, proliferation, differentiation, and mobilization. To a lesser extent, HSPCs also stimulate osteoblast secretion of leukemia inhibitory factor (LIF), thereby participating in the regulation of HSPC differentiation. HSPC-derived bone morphogenic proteins (BMP-2 and BMP-6) promote mesenchymal stem cell (MSC) differentiation into mature osteoblasts, forming a positive paracrine loop between HSPC and osteoblast development and activation. Finally, HSPCs are in direct contact with stromal cells, including CXCL12-abundant reticular cells (CARs), which may be important for cell orientation during HSPC division. Transfer of reactive oxygen species (ROS) to stromal cells through connexin-43 (Cx43)-dependent gap junctions (dotted lines) promotes HSPC survival and self-renewal.

density-dependent paracrine (quorum sensing) activities [38]. It is also widely recognized that epigenetic mechanisms regulate fundamental HSPC properties, but how self-signals are integrated with both epigenetic programs and extrinsic signals to sustain regenerative potency and self-renewal of individual clones remains unknown [39, 40].

HSPC signals directly shape the function of the hematopoietic microenvironment

Given the close spatial proximity, it is not surprising that HSPC signals regulate non-hematopoietic, heterotypic cells in the niche via paracrine mechanisms (Fig. 2). Evidence for a close interdependence may be strongest between HSPCs and osteoblasts. Several expressed or secreted factors from osteoblasts impact HSPC function including the Notch ligand Jagged 1 and IL-6 [41]. Interestingly, co-culture with CD34-positive BM cells in turn increases IL-6 and leukemia inhibitory factor synthesis in osteoblasts, but without a requirement for cell-cell contact [42]. Recently, an additional contact-dependent transfer of small membrane microdomains from HSPCs to osteoblasts was also described [43]. Enriched in CD63 and CD133, these membrane microdomains are internalized into osteoblast signaling endosomes, driving downregulation of Smad signaling, and thereby augmenting osteoblast production of CXCL12, a chemokine essential in HSPC migration and quiescence. Further promoting interdependence, HSPCs direct mesenchymal stem cell differentiation toward the osteoblastic lineage by bone morphogenic proteins BMP-2 and BMP-6 secretion, a phenomenon that is enhanced under BM stress [44]. Hematopoietic-derived osteoclasts may additionally influence HSPC mobilization and niche maintenance, though the exact mechanistic impact is uncertain [45, 46]. In part, secretion of macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL) by osteoblasts and other BM stromal cells promotes differentiation of osteoclasts from hematopoietic precursors, thereby contributing to osteoclast-driven niche remodeling. Altogether, reciprocal communication between these cells reinforces the close relationship between hematopoiesis and bone turnover.

HSPCs and mesenchymal cells also communicate directly via gap junctions [47]. Under stress, HSPC-derived connexin-43, a major constituent of gap junctions, supports the proliferative rebound following injury of HSPCs by facilitating extrusion and transfer of potentially toxic reactive oxygen species to neighboring stromal cells, thereby minimizing apoptosis or induced senescence [48].

HSPC secreted factors are also important for angiogenesis and vascular remodeling of the metabolically unique BM microenvironment. In addition to its autocrine role discussed above, HSPC secretion of ANGPT1 signals to TIE2-expressing endothelial cells [49]. Following irradiation, in vivo knockout of ANGPT1 in HSPCs and LEPR-positive stromal cells results in vascular leakiness, BM hypercellularity, and HSPC expansion [49]. In this way, HSPC-derived ANGPT1 serves to preserve stemness and an intact vasculature under stress. A similar role in remodeling the vascular niche following inflammatory stress extends to VEGF secreted by HSPCs [50]. Mice treated with IFN-α or an interferon mimetic experience a systemic inflammatory response with transient increases in endothelial cell proliferation and BM vasculature. These events are fueled by increased HSPC VEGF production and endothelial expression of the corresponding receptor VEGFR [50].

The bidirectional relationship between HSPCs and cellular components of the niche is not limited to the BM

microenvironment. During development, definitive HSPCs appear to trigger changes in the nearby perivascular fetal niche. Migration of RUNX1-positive HSPCs into intermediate hematopoietic niches (zebrafish caudal hematopoietic tissue and murine fetal liver) has illustrated the endothelial and stromal remodeling that occurs with HSPC colonization [51]. Following extravasation into the niche, HSPCs trigger the formation of a multicellular sinusoidal pocket, in a process dubbed "endothelial cuddling", which facilitates proper HSPC cell division. Direct HSPC contact with CXCL12-positive stromal cells may be required to orient HSPCs for this process [51]. Altogether, these findings reinforce a model of the HSPC niche during development and postnatal life as a highly adaptable operational unit built around bidirectional crosstalk.

HSPC signals facilitate cell-cell competition within the bone marrow microenvironment

Beyond the reviewed evidence for autocrine and heterotypic signaling, there is emerging evidence for HSPC signaling as a mechanism underlying competition between hematopoietic cells for occupancy of the BM niche. Conceptually elegant studies of the Drosophila imaginal disc first shed light on non-cell autonomous events whereby cells that differ in their respective levels of fitness can confer neighbor elimination or force differentiation. By nature, the impact of differential cellular fitness requires the capacity of cells to sense and signal to neighboring cells, using many of the molecular mechanisms discussed above [52–54]. The possibility that cell competition between HSPCs in the BM exists has been experimentally demonstrated (Fig. 3) [52, 55].

p53-mediated cell competition

A landmark study showed that DNA damage following ionizing irradiation triggered HSPC competition and selective expansion of populations with relatively lower p53 levels [55]. Cells experiencing higher p53 levels as a result of experimental DNA damage underwent senescence-like changes, leaving them marked for gradual replacement by more highly proliferative cells [56]. In this experimental system, the mechanism of cell competition was manifested by selective growth and was based on relative differences between competitors, often revealed under stress, not homeostatic conditions [55, 57]. Interestingly, such differential p53-mediated fitness phenocopies events in models of the human BM disorder Diamond-Blackfan anemia (DBA) [58]. In DBA, increased nucleolar stress from disruption of ribosomal biogenesis can lead to an overall imbalance and relative excess of proteins RPL-5 and −11 that bind to MDM2. The resulting decrease in availability of MDM2 in turn slows p53 turnover, and promotes differential fitness.

Senescent cell contribution to competition

To communicate cellular fitness and impact competitor fates, the secretome of senescent cells encompasses a broad array of chemokines, cytokines, growth factors, and proteases, referred to in aggregate as senescence-associated secretory phenotype (SASP) [59, 60]. Individually and in combination, SASP factors stimulate the growth of neighboring cells, thereby promoting physiologic tissue regeneration. For example, one report showed that the trafficking of the JAK/STAT ligand, Unpaired-3, from senescent cells caused the expansion of more fit neighboring cells [61]. Conceivably, such pro-mitogenic paracrine stimulation may be important in the gradual replacement of senescent, damaged HSPCs by stem cells emerging from quiescence following injury. It is worth noting that SASP may, in some cases, alternatively promote the paracrine spread of a senescent bystander response to other HSPCs via secreted factors such as TGF-β family members, VEGF, CCL2, or CCL20 [62]. Finally, relative expression of adhesion molecules may provide another mechanism by which HSPCs contend for physical niche space, whereby higher levels of ROBO4, CXCR4, and integrin α4β7 offer a competitive advantage in homing, engraftment, and retention over cells expressing lower levels [63, 64]. Teleologically, HSPC signaling underlying cell competition provides a means of maximizing nutrient utilization and space, elimination of compromised cells, and potentially tissue-level tumor suppression during development and adult life.

Cell competition in hematopoietic malignancies

Not surprisingly, competitive cell interactions feature prominently in the context of hematopoietic malignancy where HSPCs and leukemia cells compete for the same physical niche in the BM. Seminal studies by several groups have recently upended the notion that physical overcrowding alone drives leukemic progression and hematopoietic suppression in the BM niche. Instead, niche occupancy depends in part on the proportional balance between healthy and malignant components, and direct crosstalk between the two populations contributes to a cellular tug of war in the niche [65–67]. Under dose escalation, healthy HSPCs can not only outcompete leukemic stem cell (LSC) growth in the niche and improve survival in animal models of AML, but alter the proliferative capacity of malignant bystander cells, consistent with the possibility of cell-cell signaling between the two populations [65, 68]. Conversely, when LSCs outcompete normal HSPCs for niche space, they show gains in

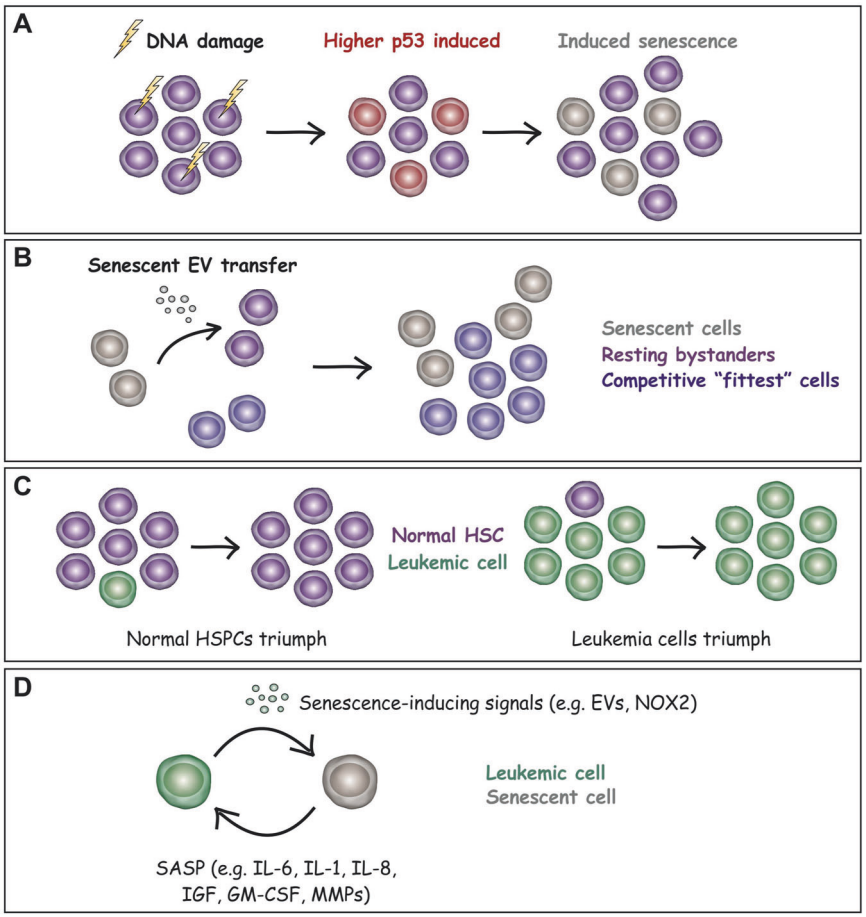

Fig. 3 Cell-cell competition drives predominance of the "fittest" hematopoietic cells. Schematics of several proposed mechanisms of cell-cell competition in the bone marrow (BM) microenironment. **a** HSPC subpopulations compete based on relative p53 levels. HSPCs harboring higher levels of p53 induced by DNA damage (e.g., irradiation) are driven toward senescent-like phenotypes, and are outcompeted by HSPCs expressing relatively lower p53 levels. **b** In some situations, senescent cells in the BM induce paracrine senescence, at least in part by transfer of biologically active extracellular vesicles (EVs), allowing non-recipient HSPCs to outcompete senescent cells. **c** In the context of malignant leukemia cells, relative proportions of normal HSPCs and leukemic stem cells (LSCs) dictate the ultimate "winners" and "losers." **d** Leukemia cells may also induce senescence in neighboring cells, including HSPCs and stromal cells, that in turn produce pro-mitogenic senescence-associated secretory phenotype (SASP) factors promoting leukemia cell growth.

chemoresistance compared to circulating leukemia cells, that potentially reflect the adhesive, immunosuppressive, and mitogenic properties acquired during cell-cell interactions in the BM niche [69].

Cell-cell competition may well reinforce the impact of genetic alterations in leukemia cells, where the loss of p53 tumor suppressor function could lead to the relative advantage over normal hematopoietic cells. Mechanistically, overexpression of the human proto-oncogene MYC, often activated in hematologic malignancies, may give rise to super-competitive leukemia cells [70]. Along with observations that AML cells can induce senescence in surrounding cells through secreted SASP factors [71], the crosstalk between malignant and non-malignant hematopoietic cells in the leukemic BM fits models and mechanisms of cell-cell competition, even as experimental confirmation in human is still lacking.

Extracellular vesicles modulate HSPC interactions in the niche

Leukemia-derived vesicles

One mode of crosstalk between leukemic cells and residual normal HSPCs is the cell-cell trafficking of EVs. Encompassing both secreted endosomal-derived exosomes and limiting cell membrane-derived microvesicles, EVs carry DNA, RNA, and protein cargo that can durably alter recipient cell behavior. Our group showed that selective microRNA (miRNA) species are highly abundant in EV populations from AML cells in culture, and in circulating vesicles from human patients or animals harboring AML xenografts [72–74]. Specifically, we showed that leukemia-derived EVs deliver select miRNAs, including miR-1246 and −1290, to HSPCs, leading to RAPTOR-mediated

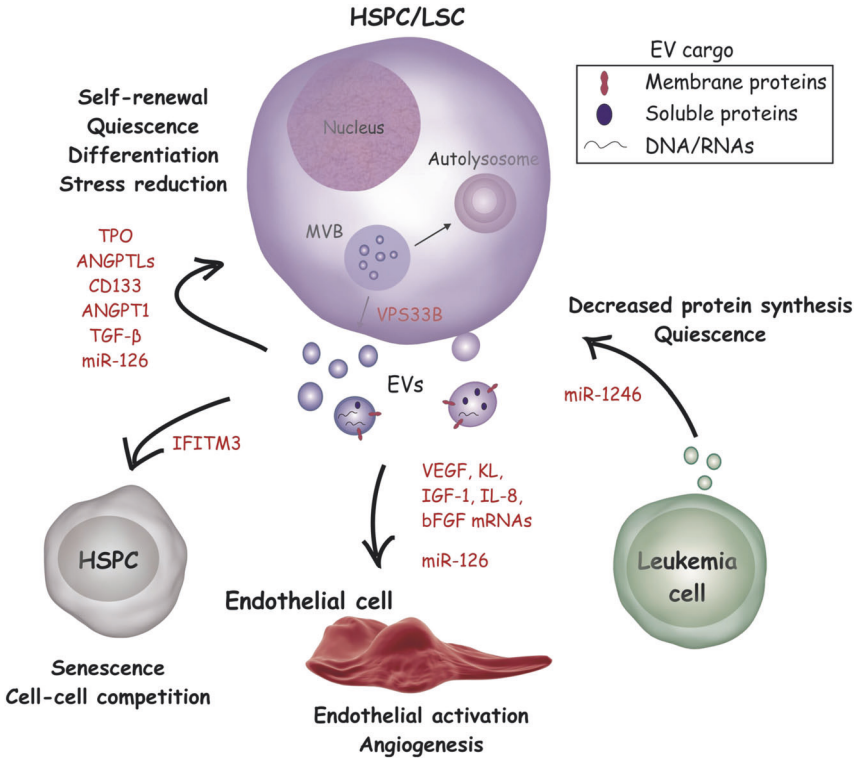

Fig. 4 Extracellular vesicles mediate crosstalk in the bone marrow microenvironment. Interplay between autophagic activity, the endosomal sorting pathway, and membrane budding results in secreted extracellular vesicles (EVs) including multivesicular body (MVB)-derived exosomes and membrane-shed microvesicles. HSPC EVs rely in part on VPS33B-mediated secretion, and contain protein, lipid, and nucleic acid (DNA, mRNA, miRNA) cargo that exert both autocrine and paracrine effects in the niche. Stemness and growth factors associated with EVs likely provide self signals regulating HSPC renewal, quiescence, differentiation, and elimination of toxic intracellular material. Secreted EVs may also mediate cell-cell competition events in the niche by inducing senescence in neighboring HSPCs with lower fitness capacity. Endothelial cell uptake of HSPC EVs results in activation, chemoattraction, and angiognesis. While the imapct of HSPC EVs on leukemic cells remains unknown, leukemia-derived EVs can induce hematopoietic suppression, in part by transfer of small noncoding RNAs such as miR-1246 to HSPCs, resulting in reduced protein synthesis and HSPC quiescence. TPO thrombopoietin, ANGPTLs angiopoietin-like proteins, ANGPT1 angiopoietin-1, TGF-β transforming growth factor β, IFITM3 interferon induced transmembrane protein 3, VEGF vascular endothelial growth factor, KL Kit ligand, IGF-1 insulin-like growth factor 1, bFGF basic fibroblast growth factor, VPS33B vacuolar protein sorting-associated protein 33B, LSC leukemic stem cell.

suppression of mTOR signaling and decreased protein synthesis while raising p53 levels, all core pathways operative in cell-cell competition [72, 75]. These findings support observations made by others that residual normal HSPCs in AML xenograft models are predominantly quiescent and generally more resistant to elimination [76]. Intriguingly, progenitor cells which are much less vulnerable to disruption of proteostasis, lose clonogenicity through RISC-mediated translational suppression of the transcription factor c-Myb by EV-contained miR-150 and −155 [74].

AML-derived EVs serve a broad array of proangiogenic, tumor-promoting, and hematopoietic-suppressive functions, and may be particularly important in maintaining LSC phenotype (Fig. 4) [72, 77]. For instance, impaired vacuolar protein sorting-associated protein 33B (VPS33B)-dependent vesicle secretion leads to loss of LSC quiescence, increased apoptosis, delayed onset of leukemogenesis, and increased survival in a murine MLL-AF9–transduced AML model [78]. Similar to its role in normal HSPCs, miR-126 promotes LSC quiescence and self-renewal through its modulation of PI3K/AKT/mTOR, thereby promoting chemotherapy resistance [79]. Given the role of EV-associated miR-126 in promoting angiogenesis, it is conceivable that LSC-derived EVs confer leukemia-supportive effects in the BM niche [80, 81]. Secretion of senescence-inducing EVs from LSCs may further suppress normal hematopoiesis in the niche, contributing to cell competition in favor of malignant and pre-malignant clones.

EVs in physiologic hematopoiesis

An extensive review of EV biogenesis is beyond the scope of this report, but a number of studies speak to a much broader role vesicle trafficking plays in regulating physiologic cell-cell communication in the BM (Fig. 4) [82]. For

example, mesenchymal cell- or platelet- derived vesicles containing adhesion and anti-apoptotic factors affect HSPC homing and survival [83–85]. However, little is known about the contribution of HSPC-derived vesicles to the function of the BM microenvironment. HSPC autocrine stemness factors including TPO and angiopoietin-like proteins (ANGPTLs) are actively recruited into VPS33B-dependent small EVs that maintain quiescence, survival, and repopulation following transplantation [78]. Other HSPC-stimulating ligands such as FLT3 ligand may also be present in membrane-bound form with functional extracellular domains [86], and conceivably secreted in association with membrane-encapsulated EVs. To date, ANGPT1, CXCR4, TGF-β, and numerous interleukin and leukocyte-specific integrin proteins have been identified in secreted vesicles [87]. The stem cell marker CD133 is also readily packaged and secreted in EVs [88], a process which aids in depletion of cellular CD133 levels and promotes HSPC differentiation. The importance of vesicle trafficking proteins (Nbea, Cadps2, and Gprasp2) for efficient hematopoietic engraftment and repopulation was recently reinforced in an in vivo shRNA screen targeting genes highly expressed in stem and progenitor cells [89].

As mentioned above, given their deep regulatory potential and frequent EV enrichment, small, non-coding RNAs have been of obvious interest to the field. During development, HSPC-derived EVs promote differentiation of embryonic stem cells into HSPCs in part by transfer of miR-126 that results in Notch inhibition [90]. In adult hematopoiesis, miR-126 appears to instead promote HSPC quiescence by limiting cell cycle progression through reduction of PI3K/AKT/mTOR activity [79, 91]. However, accumulation of miR-126-containing EVs in the BM in response to granulocyte colony-stimulating factor may drive mobilization and subsequent differentiation of HSPCs through downregulation of vascular cell adhesion molecule 1 expression on recipient HPSCs [92].

EVs secreted from HSPCs may also participate in heterotypic cell-to-cell communication in the HSPC niche. For instance, VEGF, KL, IGF-1, IL-8, and bFGF mRNAs in addition to miR-126 are enriched in small vesicles secreted from HSPCs and promote endothelial cell chemoattraction and angiogenic activity [80, 81, 93]. Packaging of other RNAs with known hematopoietic regulatory functions into EVs for cell transmission remain to be discovered.

EVs likely also play an important role in externalizing cellular content in order to retain stemness and maintain cellular integrity. For example, in conditions of heightened nuclear DNA damage, cells increase EV secretion. Inhibition of vesicle release leads to accumulation of cytoplasmic DNA and senescence or apoptosis [94]. Given the need for HSPCs to minimize genotoxic stress, EV elimination of harmful cytoplasmic DNA fragments is an attractive mechanism to guard HSPC pool integrity [95]. More broadly, EVs are critical for eliminating undesirable or toxic cell material from cells. Like autophagy and its role in HSPC self-renewal and maintenance, EV biogenesis and secretion may constitute an important mechanism of HSPC quality control [96, 97]. For instance, elimination of mitochondria in HSPCs is required to reduce reactive oxygen species and maintain quiescence; failure to do so results in cell cycle entry and differentiation [96]. Recent studies have demonstrated that mitochondrial material, including whole organelles, may be packaged into EVs for horizontal transfer. Mesenchymal stem cells in particular manage intracellular stress by packaging mitochondria into secreted microvesicles targeted to macrophages, thereby outsourcing mitophagy or mitochondrial recycling [98]. Additional investigation is needed to uncover whether analogous mechanisms are employed by HSPCs.

Recent evidence in other cellular models also suggests that EVs may serve as paracrine transmitters of a senescence phenotype in bystander cells through increasing expression of IL-8, integrin β3, and cell-cycle regulators CDKN2A and CDKN1A by transfer of interferon-induced transmembrane 3 (IFITM3) [99]. Proteomic profiling of senescent cell-derived EVs shows little overlap between known soluble factors secreted from cells, suggesting an EV- directed mechanism distinct from SASP that may be similarly employed by HSPCs.

Perspective and future directions

While most attention has focused on HSPCs as epigenetically programmed units, it is clear that the cell-autonomous activity of HSPCs does not stop at the cell membrane, but also involves secretory pathways to self-communicate and actively remodel the microenvironment. These cellular activities are bound to impact self-renewal, differentiation, and clonal expansion under homeostatic conditions, and in the context of aging, stress, and malignancy. Importantly, emerging differences between heterogeneous populations of hematopoietic stem and multipotent progenitor cells have recently challenged the traditional perspective of compartmentalized, hierarchal hematopoietic development [1]. Variance in self-renewal capacity, differential mature lineage output, and ability to secrete and respond to cytokine stimuli may explain how distinct HSPC subsets propagate clonal trajectories during serial transplantation [1, 100]. Given the emerging evidence of early lineage demarcation and shared cellular transcriptional networks at various stages of HSPC development, categorical distinctions between stem and progenitor cell populations may be blurred. HSPC

subpopulations also likely engage in direct crosstalk as they orchestrate lineage-commitment and maturation, though subset-specific communication remains to be determined.

The available evidence suggests that a better understanding of HSPC cell interaction and the mechanisms underlying cell-cell competition in the niche may have broad implications in advancing knowledge of age-associated changes in immune function, referred to as senescent immune remodeling (SIR) [101]. Interestingly as mice and humans age, a bias of HSPC differentiation toward the myeloid lineage and a relative reduction in common lymphoid progenitor cell differentiation is generally apparent [102]. An overall reduction in the size of the HSPC pool is concomitantly noted [103]. In part, we hypothesize that SIR may rely upon cell-cell competition amongst HSPCs harboring intrinsic myeloid or lymphoid bias, such that populations of disadvantaged cells make room for, and even support, the growth of other HSPCs. The resulting restriction in clonal diversity of HSPCs may in turn drive clonal hematopoiesis of indeterminate potential and potential pre-malignant states [104]. Accordingly, HSPC signals may also play a role in the remarkable stability of epigenetically programmed clonal trajectories that transfer fundamental traits such as regenerative capacity and time to exhaustion in models of murine serial recipient transplantation [40, 105].

It is conceivable that harnessing the mechanisms and mediators underlying HSPC-niche crosstalk could be exploited for therapeutic gain. Further insight into autocrine and paracrine signals employed by HSPCs in processes of self-renewal and divisional symmetry could facilitate improvements in laboratory HSPC expansion, perhaps through manipulation of important regulators of repopulation activity. Beyond the research implications, ex vivo HSPC expansion could be used to overcome the numerical limitations in allogeneic transplant grafts or autologous gene therapy products.

Finally, the roles of EVs in mediating BM cell-cell interactions is an emerging topic of great interest. Selective manipulation of HSPC- or LSC-derived EV cargo secretion may confer potential therapeutic strategies for de novo hematologic malignancies or relapse conditions. It is also increasingly recognized that suppression of normal hematopoiesis by leukemic cells involves secretion of soluble or vesicle-associated modulatory factors. Adjuvant treatments that improve the resilience of HSPCs and contribute to resetting physiologic conditions in a leukemic niche have the potential to profoundly impact outcomes of leukemia treatment. Future studies further elucidating the active roles HSPCs employ in shaping their BM niche will certainly advance hematopoiesis and stem cell research and inform therapeutic strategies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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