Mechanoregulation in Hematopoiesis and Hematologic Disorders

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Abstract

Purpose of Review Hematopoietic stem cells (HSCs) are reliant on intrinsic and extrinsic factors for tight control of self-renewal, quiescence, differentiation, and homing. Given the intimate relationship between HSCs and their niche, increasing numbers of studies are examining how biophysical cues in the hematopoietic microenvironment impact HSC functions.

Recent Findings Numerous mechanosensors are present on hematopoietic cells, including integrins, mechanosensitive ion channels, and primary cilia. Integrin-ligand adhesion, in particular, has been found to be critical for homing and anchoring of HSCs and progenitors in the bone marrow. Integrin-mediated interactions with ligands present on extracellular matrix and endothelial cells are key to establishing long-term engraftment and quiescence of HSCs. Importantly, disruption in the architecture and cellular composition of the bone marrow associated with conditioning regimens and primary myelofibrosis exposes HSCs to a profoundly distinct mechanical environment, with potential implications for progression of hematologic dysfunction and pathologies.

Summary Study of the mechanobiological signals that govern hematopoiesis represents an important future step toward understanding HSC biology in homeostasis, aging, and cancer.

Keywords Biomechanical force · Hematopoietic stem cells · Hematopoiesis · Hematological disorders · Mechanobiology · Mechanosensors

Introduction

Hematopoietic stem cells (HSCs) are a rare population of cells capable of self-renewal that are responsible for establishment and maintenance of the blood system [1]. Due to the relatively short lifespan of many mature types of blood cells, HSCs are necessary to replenish these cells throughout

the lifetime of the individual in a process termed hematopoiesis [2]. Their capacity to self-renew and differentiate into multiple blood lineages long-term separates HSCs from committed progenitor cells, whose differentiative potential is generally restricted to a few or a single lineage and usually exhausts after a few weeks [3]. It is because of the HSC's self-renewal capability that HSC transplantation, the standard of care for most hematologic malignancies and bone marrow failure syndromes, is possible [4]. Yet, clinical success following HSC transplantation continues to be limited by high rates of morbidity and mortality. This challenge has motivated extensive improvements in donor recruitment and matching [5], aggressive pursuit of alternative sources of HSCs, and further exploration into the basic mechanisms that regulate HSC engraftment and function in the bone marrow. Thus, understanding the intrinsic and extrinsic factors that regulate HSC functions has emerged as a major objective for the field, with wide-ranging implications for HSC biology, treatment of hematologic malignancies, and transplantation medicine [6–8].

Studies in recent years have revealed that HSCs are functionally heterogeneous, and intense interest surrounds how

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this variability is determined [9–11]. Researchers have looked for clues in the transcriptional and epigenetic machinery of HSCs and within the stem cell niche [3, 12]. HSCs reside predominantly in the bone marrow, though they are also known to circulate through the vasculature during embryogenesis and later in adulthood following a circadian pattern [12, 13]. The bone marrow is a complex organ that houses hematopoietic and non-hematopoietic cells interwoven with vasculature and sympathetic nerves (Fig. 1a) [3, 9]. The marrow provides a stem cell niche vital for HSC maintenance, differentiation, trafficking, and

response to stress [3, 9, 14]. Several cell types contribute to and regulate the niche, including non-hematopoietic cells like osteoblasts, mesenchymal stem and progenitor cells, endothelial cells, adipocytes, and nerve cells, as well as hematopoietic cells such as macrophages, osteoclasts, megakaryocytes, T lymphocytes, and neutrophils [9, 14, 15]. Localization of HSCs within distinct areas of this microarchitecture has been thought to be key to identifying the critical cues that define subpopulations of HSCs with different lineage potential and self-renewal capacity. Consensus on where HSCs are most highly enriched has

Fig. 1 Bone marrow architecture and mechanoregulation. **a** The bone marrow is composed of a complex milieu of cells interlaced with blood vessels and nerves, working in concert to support hematopoiesis. An emerging concept in the field is that the marrow houses distinct hematopoietic niches for subpopulations of HSCs with functional heterogeneity. **b** Integrins, mechanosensitive ion channels, and primary cilia sense mechanical features of the hematopoietic niche. Activation of mechanotransduction pathways alter gene expression and cell behavior critical for homeostasis and response to stress

been elusive, with some reports suggesting that HSCs preferentially home to and reside in perivascular endosteal regions near the bone, while others suggest arteriolar or sinusoidal enrichment of HSCs [3, 14]. Still, others point to random perisinusoidal distribution throughout the central marrow cavity [16]. The holy grail of identifying the HSC niche is so important because it could point to candidate biochemical factors crucial to hallmarks of stemness. Emerging evidence from the stem cell field also suggests that HSCs could encounter distinct mechanical properties in various niches within the marrow, including different matrix elasticity, nanotopography, microgeometry, and biomechanical forces that regulate cell fate and function [7, 8, 17, 18]. While much is known about key molecular signals in the bone marrow niche, far less is known regarding the effects of mechanical cues on HSC function. Given the intimate relationship between HSCs and their niche, increasing numbers of studies are examining mechanobiological cues and their impact on HSC functions.

While it is well documented that bone cells, and specifically osteocytes, are mechanosensitive, recent studies have found that hematopoietic cells are able to sense external forces as well. The marrow is responsive to geometric properties, matrix stiffness, and mechanical forces within the microenvironment that are associated with a heterogeneous population of cells and blood flow within the arterial vessels and highly branched sinusoidal capillaries of the bone marrow [7, 19]. Detailed flow profiles for marrow vessels and capillaries implicate shear stress as an important factor in hematopoietic stem and progenitor cell homing [19]. Bone loading, such as that caused by ambulation, can also stimulate changes in shear stress within the marrow and can induce mechanical stress which promotes increases in the expression of cyclin D1 and proliferation of marrow cells [20]. These findings are supported by our own work illustrating that wall shear stress generated by blood flow acts on hemogenic endothelial cells, the precursors of HSCs in the developing embryo, to trigger elevated rates of proliferation, decreased apoptosis, and increased long-term engrafting activity and multipotency of emerging hematopoietic stem and progenitor cells [21, 22]. Collectively, these studies provide strong evidence for the idea that extrinsic forces elicit changes in the transcriptome and proteome of hematopoietic cells. As irregularities in either self-renewal or differentiation can lead to myeloproliferative disease, leukemia, or cytopenia, tight regulation of the signaling that controls these processes is essential [3, 14].

In this review, we provide an overview of our current knowledge of mechanical regulation in adult HSCs. We discuss critical mechanosensors found in hematopoietic cells and the mechanotransduction pathways that are activated by these sensors. Lastly, we consider the implications of altered mechanical cues for hematologic pathologies and how these features of the niche could exacerbate or drive disease progression.

Mechanosensors and Mechanotransduction

Hematopoietic cells are exposed to a dynamic biochemical and biophysical environment whether they are sheltered in the bone marrow or trafficking through the vasculature or other tissues [7]. The mechanical properties of the microenvironment can have a significant impact on HSC behavior [7, 23, 24]. Indeed, the ability to recognize and respond to extrinsic mechanical forces allows stem cells to adapt during normal developmental processes and in response to aging, inflammation, injury, infection, and other pathological insults [25, 26].

All cells, including HSCs, rely upon mechanosensors to detect physical features or phenomenon external to the cell, such as fluid movement or elasticity of the latticework of collagens, glycoproteins, and proteoglycans that form the extracellular matrix (ECM) [27, 28]. Cells also rely on mechanosensors to detect tension and pressure across tissues or between cells. Integrins and other cell adhesion molecules, A Disintegrin And Metalloproteases (ADAMs), G protein-coupled receptors, ion channels, caveolae, glycocalyx, and primary cilia have all been implicated as potential mechanosensors in HSCs and hematopoietic cells [29] (Table 1). A primary function of mechanosensors is to detect and activate pathways that transform biophysical cues into biochemical signals, ultimately leading to changes in cellular behavior [7, 27]. The capacity of a cell to transduce external forces into biochemical signals is referred to as mechanotransduction [25, 26, 30]. Here, we detail our most recent knowledge of the most well-established mechanosensors in hematopoiesis, the integrins, as well as two other plasma membrane-based sensors with emerging roles in blood cell development.

Integrins

The integrin family of cell surface receptors is transmembrane heterodimeric receptors composed of an α - and β -subunits that adhere to ECM and neighboring cells [31, 32]. Signaling through integrins is regulated by conformational change and their activation can be triggered either from the outside-in or the inside-out [29, 33]. The extracellular domain binds ECM ligands, membrane-anchored integrin counter receptors such as V-CAM1 and I-CAM1/2, cytokines, and growth factors [34–36] (Fig. 1b). The intracellular domain recruits linker proteins such as talin, kindlin, vinculin, and paxillin that join the integrin receptor and the actomyosin cytoskeleton, acting as a scaffold for downstream signaling pathways [35, 37]. This allows integrins to relay information from the ECM into the cell, enabling mechanoperception of compressive and tensile forces, followed by adaptations in cell behavior [23]. Their ability to sense mechanical changes in the microenvironment makes integrins vital mechanosensors [32].

In HSCs, integrins play critical roles in proliferation, maintenance, and homing. Indeed, integrins are the primary

Table 1 Mechanosensors and mechanosensitive signaling pathways in hematopoiesis

Mechanosensors	Functions in hematopoiesis	Interactions	Downstream	References
Cell adhesion molecules				
Integrin $\beta 7$	Homing and long-term reconstitution	ECM, MAdCAM-1		Murakami et al. 2016 [40]
Integrin $\alpha 3$	HSC long-term engraftment potential		TAZ	Tomellini et al. 2019 [65]
Integrin $\alpha 5$	Proliferation, quiescence	Periostin, fluid shear stress	FAK, PI3K/Akt	Khurana et al. 2016 [34]
Integrins $\alpha 2\beta 1$, $\alpha 4\beta 1$, $\alpha 5\beta 1$, $\alpha 6\beta 1$, $\alpha 4\beta 7$, $\alpha 9\beta 1$, $\alpha 11\beta 3$	Homing, self-renewal, proliferation, survival, differentiation	ECM, fluid shear stress	FAK, SFK, MAPK	Levesque and Winkler 2016, Braicu et al. 2019 [39, 62]
PECAM/CD31	Endothelial and hematoendothelial specification	VE-cadherin, fluid shear stress	VEGFR2, integrins, PI3K	Tzima et al. 2005 [86]
Ion channels and ions				
Transient receptor potential (TRP), TRPC1, TRPV4	Differentiation of megakaryocytes, dendritic cell phagocytosis, motility and proliferation of leukemia stem cells	Membrane stretching, polycystin-2	Protein kinase C, nuclear factor of activated T cells	Ramanathan et al. 2016, Cabanas et al. 2018, Naert et al. 2019 [46, 87, 88]
Piezo1	Vascular remodeling, erythrocyte volume homeostasis, thrombus formation by platelets	Hemodynamic force, shear stress, mechanical stretch		Ranade et al. 2014, Ilkan et al. 2017, Cahalan et al. 2015 [89–91]
PKD1, PKD2	Megakaryocyte cytoskeletal dynamics and polarization, thrombopoiesis, quiescence of HSCs	Fluid shear stress	PAK/LIMK/cofilin, Akt, Reactive oxygen species	Hu et al. 2017, Geue et al. 2019 [92, 93]
Intracellular Ca^{2+}	HSC proliferation, differentiation, maintenance	TET enzymes, calmodulin	Mitochondria, Calmodulin-dependent protein kinase II/IV	Thm et al. 2019 [45]
A disintegrin and metalloprotease (ADAM) family				
ADAM8	Release of first erythrocytes into blood stream	Fluid shear stress	Degradation of ECM	Iida et al. 2010 [94]
ADAM10	Quiescence, differentiation, marginal zone B cell development	Notch	Notch intracellular domain activation	Gibb et al. 2010, Gibb et al. 2011, Yoda et al. 2011 [95–97]
G protein coupled receptors (GPCR)				
EP2 and EP4 $\text{G}\alpha_s$	Self-renewal and expansion	Fluid shear stress, Prostaglandin E_2	cAMP, Wnt/ β -catenin	Goessling 2009, Goessling et al. 2011, Diaz et al. 2015 [22, 98]
CaSR	Cell adhesion and lodgement	Ca^{2+} , Integrins	Integrins	Lam et al. 2011, Tharmalingam et al. 2011 [99, 100]
Other sensors and signaling effectors				
Primary cilia	HSC specification	Fluid shear stress	Notch, Hedgehog	Singh et al. 2016, Liu et al. 2019 [47, 53]
Glycocalyx	Expressed on HSCs and progenitors	Fluid shear stress	Clustering of integrins, cytoskeleton	Hemmorantaa et al. 2007 [101]
Caveolae	HSC self-renewal and quiescence	Integrins	Reactive oxygen species	Bai et al. 2014 [102]
Myosin II	HSC morphology, proliferation	Cell adhesion molecules	Rho GTPases	Choi et al. 2017 [41]
Rac1	HSC homing and migration	PRK1	Degradation of ECM	Chen et al. 2016 [61]
Nitric oxide synthase	HSC emergence and expansion	Fluid shear stress	Klf2a, NO	Adamo et al. 2009; North et al. 2009 [21, 103]

CaSR calcium sensing receptor, *ECM* extracellular matrix, *FAK* focal adhesion kinase, *LIMK* LIM kinase-1, *MAdCAM-1* mucosal addressin cell adhesion molecule-1, *NO* nitric oxide, *PAK* p21-activated kinase, *PKD* polycystin, *PRK1* protein kinase C-related kinase 1, *SFK* Src family kinase, *TET* ten eleven translocation, *TRPC1* transient receptor potential cation channel subfamily C member 1, *TRPV4* transient receptor potential Vanilloid type 4

proteins responsible for establishing cell-ECM interactions and are widely expressed in HSCs [25, 26, 29, 38]. Some of the most well-characterized integrins expressed by HSCs and progenitors are integrins $\alpha 4\beta 1$ (CD49d/CD29 complex or VLA-4) and $\alpha 5\beta 1$ (CD49d/CD29 complex or VLA-5) but can include other integrin heterodimers such as $\alpha 2\beta 1$, $\alpha 6\beta 1$, $\alpha 4\beta 7$, $\alpha 9\beta 1$, and $\alpha \text{IIb}\beta 3$ [39]. Integrin-ligand adhesion is critical for homing and anchoring of HSCs and hematopoietic progenitor cells in the bone marrow niche [39]. Evidence demonstrates that expression of $\beta 7$ integrin on HSCs promotes improved long-term engraftment and better homing to the bone marrow through its interactions with the endothelial ligand mucosal addressin cell adhesion molecule-1 (MAdCAM-1) [40]. Also, interactions between the ECM protein periostin and integrin- αv suppress HSC proliferation by inhibiting FAK/PI3K/AKT, ultimately resulting in improved maintenance of quiescence in HSCs [34].

From a bioengineering perspective, integrins are particularly attractive candidate mechanosensors for manipulation given their known importance in HSCs and the ease of fabricating bioinspired ECM in culture platforms. Engagement of integrins with bone marrow-mimetic matrix substrates affects the morphology, proliferation, and myeloid lineage specification of HSCs [41]. Changes in matrix stiffness and ligand type modify HSC behavior through integrin-myosin II interactions [41]. Ongoing efforts to construct biomimetic platforms that recapitulate various HSC niches found in development and in the adult bone marrow should be focused on better understanding cell adhesion molecules like integrins and how they transform physical cues into changes in cell behavior. Following introduction of two lesser understood mechanosensors found on hematopoietic stem and progenitor cells, we revisit integrin-associated proteins and downstream effectors of integrin signaling further below.

Ion Channels

The role of mechanosensitive ion channels in stem cell biology has only recently come into view [42]. Upon sensing a mechanical stimulus, the channel undergoes a conformational change that opens the pore, allowing ions to flow through (Fig. 1b) [27]. Mechanical force directly gates these ion channels, and this allows a mechanical stimulus to quickly go from a local signal to a global cellular response [27]. It is likely that mechanosensitive ion channels are the first to respond to mechanical forces [27]. Piezo and the transient receptor potential channels (TRPs) are broadly expressed and have been the most well studied of the identified mechanosensitive ion channels [42]. Piezo and TRPs are both non-specific cation channels; however, calcium seems to be the primary downstream effector of ion channel activation [42–44]. Calcium is a potent second messenger that can influence stem cell proliferation, differentiation, and maintenance [42, 45]. Low intracellular

calcium levels in HSCs improve their maintenance in vitro through the stabilization of ten eleven translocation (TET) enzymes. While the function of mechanosensitive ion channels has been explored in other stem cells, their role in HSCs has not been carefully examined. However, TRP channels, including TRPC1, are expressed by HSCs and hematopoietic progenitors during differentiation [46], but there remains much to be determined regarding their specific function. Future research should be aimed at how these ion channels impact HSC differentiation and their switch from quiescence to activation.

Primary Cilia

Primary cilia are microtubule-based organelles that are found on the plasma membrane of many eukaryotic cells [47, 48]. Cilia act as important sensory organelles that are capable of modulating proliferation, differentiation, and cell migration [48–50]. Upon exposure to an external force, the cilia bend, activating downstream signaling pathways (Fig. 1b) [48, 51]. While it is widely accepted that primary cilia are mechanosensitive, the mechanisms regulating this ability are still under debate [51]. It is interesting to note that TRP channels are often found on primary cilia [51]. TRP channels therefore could contribute to mechanoperception in these organelles. Primary cilia are found on the majority of peripheral blood and bone marrow cells [47]. Moreover, when these cells are treated with the Sonic Hedgehog ligand, downstream effectors of the Hedgehog pathway are released from the cilia to activate target genes [47]. This is significant because Hedgehog signaling plays a vital role in early hematopoietic development [52]. Whether mechanical stimulation is sufficient to induce a similar activation of Hedgehog signaling is yet unclear but is an intriguing possible mechanism for regulation of this developmental pathway. Interestingly, primary cilia also appear to regulate hematopoietic stem and progenitor cell specification from hemogenic endothelial cells in zebrafish [7]. Primary cilia in endothelial cells were shown to transduce Notch signals [53]. Like the Hedgehog pathway, the Notch signaling pathway is critical for the development of the hematopoietic system [7, 50, 54]. More evidence is needed to determine the functions of primary cilia in HSCs, though recent studies [53] seem to demonstrate an important role for cilia in embryonic hematopoietic development.

Integrin Adhesome and Downstream Signaling

Upon activation or sensing of mechanical force, integrins cluster and nucleate hundreds of adaptor and signaling molecules at their cytoplasmic tails to form a macromolecular structure that is termed the integrin adhesome [36]. The

adhesome is a three-tiered laminated structure composed of the plasma membrane-bound integrin activation and signaling module, force transduction module, and the actin regulatory module [55]. Mechanosensing proteins such as vinculin, talin, kindlin, and paxillin are some of the major components of the force transduction module of the adhesome and can undergo conformational change or post-translational modifications in response to tensile force [25, 29, 32]. Importantly, vinculin, kindlin, and talin are all essential for proper environmental sensing by hematopoietic cells [29, 56, 57]. For example, methylation of talin dampens force transmission to integrins, resulting in increased adhesion turnover that facilitates extravasation of dendritic cells and neutrophils [58]. Kindlin-3 is highly expressed in hematopoietic cells, and its mutation causes hallmark symptoms of leukocyte adhesion deficiency type III, including hemorrhaging, anemia, leukocytosis, and loss of HSCs and progenitor cells from the bone marrow [57]. Kindlin-3 deficiency impairs retention of proliferating HSCs and progenitors in the bone marrow, but does not affect homing or retention of the most primitive quiescent HSCs, suggesting that other adhesion molecules like CD44, selectins, or N-cadherin might compensate for the absence of active integrins [59].

Nanoclusters of integrins and associated complexes can organize to form dynamic macromolecular complexes with strong mechanical linkages to the actomyosin cytoskeleton, increasing force transmission across integrins and activating catalytic activity and signaling of focal adhesion kinase (FAK) and p130Cas [36]. In association with strengthening of integrin adhesion, Src family kinases (SFKs) become activated and bind to the cytoplasmic tails of integrins or to FAKs [29]. SFKs can phosphorylate FAKs and these interactions are necessary for regulating Rho-family GTPases [29, 32, 38]. The Rho-family GTPases are vital for mechanotransduction and help cells adapt to their changing environment [29, 60]. Rho GTPase activity is tightly regulated by guanine exchange factors (GEFs), many of which are activated by FAK. Rho GTPases are important for HSC migration, proliferation, and self-renewal [29]. Rac1, a member of the Rho-family GTPases, is necessary for HSC interactions with the niche and is essential for HSC homing and migration [29, 61]. Activation of the Rho GTPase signaling cascade represents one of the possible pathways that can be activated by biomechanical force. However, there are many additional pathways that can transduce mechanical forces.

One of the most well-studied pathways downstream of integrin signaling is the mitogen-activated protein kinase (MAPK) pathway [32]. MAPK signaling acts as a bridge between extracellular signals to intracellular responses [62]. This evolutionarily conserved pathway is critical for regulating proliferation, survival, and differentiation [32]. For example, extracellular regulated MAP kinase (ERK, aka MAPK1), which is involved in MAPK signaling, is necessary to prevent

HSC exhaustion and controls HSC reentry into quiescence [63]. Another integrin-mediated mechanosensing pathway is the Hippo signaling network [32]. The main components of the Hippo pathway in the context of mechanotransduction are the Yes-associated protein (YAP) and the transcriptional co-activator with PDZ binding motif (TAZ) [29, 32]. YAP and TAZ are major players in mechanotransduction because of their ability to transduce mechanical signals into the nucleus [29, 64]. Genes involved in the Hippo pathway, including TAZ (WWTR1), are upregulated in integrin $\alpha 3^+$ long-term reconstituting primitive HSCs from human cord blood [65]. YAP is expressed in LT-HSCs [29], but currently, its importance in normal hematopoietic function remains to be determined.

While progress has been made in the effort to elucidate mechanisms of mechanotransduction in HSCs, there is still a significant gap in our knowledge. More work needs to be done to understand how HSCs sense and respond to their changing environment. Understanding these processes could lead to important insights into regenerative medicine and disease progression. Below, we discuss the effects of hematopathology on the bone marrow microenvironment and the implications of an altered biomechanical niche on blood system dysfunction.

Pathogenic Mechanisms and Significance

Mutant hematopoietic cells are able to reprogram their surrounding niche to support disease progression [66]. The disrupted niche in turn secretes factors that favor the survival and expansion of these aberrant cells, resulting in a malignant “self-reinforcing niche” [29, 66–69]. In this way, the niche can be hijacked to disadvantage healthy HSCs and ultimately lead to bone marrow failure and other hematological disorders [66]. One such disorder is primary myelofibrosis (PMF), a rare, but aggressive clonal myeloproliferative neoplasm caused by driver mutations in the *JAK2*, *MPL*, or *CALR* genes which results in bone marrow fibrosis, extramedullary hematopoiesis, increased circulating CD34⁺ cells, anemia, and inflammation [70, 71]. As the disease progresses, it causes bone marrow and organ failure, associated with osteosclerosis, extramedullary hematopoiesis in organs such as the spleen and liver, and splanchnic vein thrombosis [72, 73]. In approximately 20% of patients, PMF will ultimately transform into acute leukemia [70, 74]. Most patients die before complete leukemic transformation because of other complications associated with the disease [74]. Hallmarks of PMF include profound changes in bone marrow stroma as evidenced by myelofibrosis, neoangiogenesis, and osteosclerosis [71]. These transformations promote PMF progression by causing abnormal hematopoiesis and mobilizing HSCs into the peripheral blood [67]. The malignant changes in the niche have led

researchers to investigate the factors or cell types driving this evolution. Leptin receptor-expressing (*Lepr*⁺) mesenchymal stromal cells (MSCs) have recently been identified as the origin of myofibroblasts, the drivers of fibrosis in PMF [75]. In this study, *Lepr*⁺ MSCs expanded during PMF progression due to an increase in platelet-derived growth factor (PDGF) secreted by hyperplastic megakaryocytes [75]. Importantly, a major diagnostic criteria for PMF is the presence of excessive reticulin and/or collagen fiber deposition in the marrow [76]. It is tempting to speculate that altered niche stiffness associated with pathologic ECM deposition contributes to changes in mechanobiological signaling which reinforce PMF disease progression. Currently, however, this concept remains to be directly tested. PMF is one potential pathology that can arise from mutations in the HSC; however, other pathologies can result from our efforts to treat these hematologic malignancies.

Allogeneic stem cell transplant is the standard of care for many malignant and nonmalignant hematologic disorders. Chemotherapy and radiation are used to provide complete immunoablation to prevent graft rejection and to reduce the tumor burden in patients prior to receiving an HSC transplant [77]. High-dose myeloablative, reduced intensity, or nonmyeloablative regimens are used to classify the different preparative regimens available to patients [77, 78]. The regimen a patient receives depends on a variety of factors including age, comorbidities, and remission status at time of transplantation [77, 78, 79]. While the antitumor and myeloablative effects of these conditioning regimens are beneficial, exposure to even low-dose irradiation can have significant deleterious effects, including an increased risk for cancer [80–82]. After exposure to radiation, two different injuries can occur: acute or residual [81]. An acute injury occurs from exposure to a moderate dose of radiation [81]. It is typically transient and mainly impacts progenitor cells and other rapidly proliferating cells [81]. Residual injury, however, is characterized by a decrease in the HSC pool, HSC fitness, and impairment of HSC self-renewal [81, 82]. Damage caused by chemotherapy and radiation is also relevant where preparative regimens can remodel the bone marrow niche [81, 82]. There is damage to the bone marrow stroma that can negatively impact function of radioresistant HSCs and progenitors, as well as the ability of a hematopoietic graft from a donor to reconstitute the blood system. Chemotherapy, for example, can decrease the self-renewal capability of MSCs, which compose much of the bone marrow niche, and promote their differentiation into adipocytes and chondrocytes [83]. These modifications can lead to reduced levels of cytokines necessary for HSC maintenance and homing, including SCF, CXCL12, and VCAM-1 [83]. Ultimately, this results in perturbed hematopoietic reconstitution and increased HSC apoptosis [83]. MSCs also undergo changes in their mechanical properties as they differentiate. In the days to weeks following radiation or chemical injury to the

marrow, MSCs are primed for adipogenesis and a dramatic expansion of adipocytes throughout the long bones is observed [84]. Adipocytes do not have a dense cytoskeleton and are substantially less stiff than MSCs [85]. Thus, it would be intriguing to examine mechanotransduction signaling in the niche cells of preconditioned marrow and in the newly grafted donor HSCs of patients undergoing this type of therapy.

Conclusions

A growing body of research demonstrates the importance of biomechanical cues in maintaining normal HSC function. Together, cellular components and mechanical properties of the microenvironment control HSC quiescence and the fate of their progeny. Disorders and preconditioning modalities that disrupt bone marrow architecture and cellular composition of the niche are likely to expose the HSC to a profoundly distinct mechanical environment. More work is needed to identify the specific sensors that are crucial for regulating HSC function and how they alter cell cycling, self-renewal, homing, and lineage potential. While the mechanobiological signals that govern and/or exacerbate hematologic conditions are still poorly understood, this area of research represents an important future step in the field of hematology.

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Compliance with Ethical Standards

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

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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