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The aging hematopoietic stem cell niche: a mini review

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Hematopoietic stem cells (HSCs) undergo a functional decline during aging. The intrinsic characteristics of aged HSCs have been well-described and include a strong myeloid bias, an increase in total number, and a decrease in functionality during transplantation. The impact of the aged bone marrow microenvironment, or niche, on HSCs is less well understood. It is critical to understand the changing condition of the niche during aging, and its ability to support HSCs, as this could reveal the very signals and mechanisms needed to improve HSC fitness. Furthermore, heterochronic transplantation provides an approach to test the influence of an aged recipient niche on young donor HSCs, and conversely, of a young recipient niche on aged donor HSCs. Importantly, these experiments demonstrated that donor HSC engraftment is reduced if the recipient niche is aged, and conversely, the young niche can rejuvenate aged donor HSCs. Here we will focus on the interactions between aged HSCs and their microenvironment. We will highlight current controversies, research gaps, and future directions.

KEYWORDS

aging, hematopoietic stem cells, niche, inflammation, microenvironment, immune function, endothelial cells, mesenchymal stromal cells

Introduction

The aged hematopoietic compartment is characterized by skewed differentiation towards myeloid lineages and decline in normal cellular functions. These aging-associated abnormalities occur in the primitive HSCs, as well as in terminally differentiated immune cells (1, 2). Aged HSCs undergo phenotypic expansion but show reduced reconstitution and self-renewal capabilities upon stress (3–5). The proportion of myeloid-biased HSCs (my-HSCs) is increased during aging, leading to decreased lymphopoiesis, primarily in B cells, and diminished adaptive immunity; this is concomitant with increased myelopoiesis and incidence of myeloid malignancies (6–8). The essential role of my-HSCs in driving aged hematopoietic phenotypes is supported by a recent report, showing that antibody-mediated depletion of my-HSCs in aged mice rejuvenates the hematopoietic compartment and restores some features of youthful immunity (9).

Reciprocal transplants have shown that aged HSCs and progenitors transplanted into young recipients can partly reverse the aging phenotype (10–13). Conversely, young HSCs and progenitors can adopt an aged phenotype when transplanted into aged recipients (14). This provides strong evidence that the bone marrow (BM) microenvironment has a significant impact on HSCs throughout the lifespan. There is still controversy related to both the changes in niche cell numbers and their spatial distribution in the BM during aging that will be discussed in further detail below (15–21).

Aged HSCs exhibit distinct physical properties and molecular hallmarks. They can be sufficiently distinguished from young HSCs using deep machine-learning techniques based solely on their morphology (22). When transplanted, aged HSCs lodge further from the endosteum after homing (23, 24). In addition, aged HSCs display molecular hallmarks in comparison to young HSCs, including elevated small Rho GTPase Cdc42, loss of protein polarity (23), and altered epigenetic architecture (1). Although it remains unclear how these molecular alterations contribute to dysregulated HSC functions, targeting elevated Cdc42 via its specific inhibitor is shown to rejuvenate aged HSCs (23).

Megakaryocytes are an important component of the HSC niche and are thought to regulate HSC quiescence by secreting various factors, including CXCL4 (25–27). Analysis of the spatial relationship between HSCs and megakaryocytes has shown that HSCs are significantly closer to megakaryocytes in the niche, further supporting a functional relationship between the cell types (20, 25). Multiple studies have shown that megakaryocytes and megakaryocyte progenitors (MkP) expand in aged BM (14–17, 20). One hypothesis is that an increased distance between HSCs and megakaryocytes during aging contributes to loss of quiescence. However, there is still not a consensus on whether the distance between HSCs and megakaryocytes significantly changes during aging; some approaches show an increase (15, 17), while others do not (20).

Downregulation of DNA repair pathways cause early onset of aging-like phenotypes in mouse and human (28–30), suggesting that DNA damage and accumulation of DNA damage contribute to aged HSC phenotypes, for example, increased incidence of Clonal Hematopoiesis of Indeterminate Potential (CHIP) (31). CHIP refers to the expansion of peripheral blood cells derived from HSCs with at least one somatic driver mutation in healthy elderly individuals (32–34). CHIP is strongly linked to aging and confers an increased risk for blood cancers, non-hematological diseases (e.g., cardiovascular disease), and all-cause mortality (32–35). There is an approximately 2-3-fold increase in mutation frequency in aged HSCs (36, 37). However, such a linear increase in the frequency over time does not correlate with the exponential increase in CHIP and myeloid leukemia seen in the elderly. Mathematical modeling of HSC aging based on evolutionary theories further suggests that accumulation of DNA damage in HSCs is insufficient to alter HSC fitness (38, 39). Rather, these models suggest that extrinsic mechanisms in aged BM microenvironment are the major selective driving force for aging-associated CHIP and myeloid leukemia. This hypothesis is supported by the known roles of different BM microenvironment cell types in regulating adult HSC functions as detailed below.

Clonal hematopoiesis is associated with aging and leukemia initiation, and therefore must be studied in the context of the aged niche. Using a pool of transduced donor hematopoietic progenitor cells, Vas et al. found that transplantation into aged recipients reduced clonality compared to young recipients (40). This study also found that transplant of hematopoietic progenitor cells into an aged microenvironment produced the characteristic increase in myeloid and decrease in lymphoid cell output associated with aged HSCs.

Immune cells

HSCs and terminally differentiated immune cells exhibit functional decline during aging, as well as significant changes in lineage output (i.e, reduction or expansion of certain subsets). Aged immune cells are the main contributor to “inflammaging”, which refers to unresolved BM microenvironment and systemic inflammation in the absence of pathogens, through secreting inflammatory cytokines (41, 42). One example is IL-1 produced by myeloid cells that increases during aging, creating a vicious cycle of *Tet2*$^{+/-}$ clonal expansion that contributes to CHIP via increased HSPC proliferation (31). Similarly, chronic inflammation induced with IL-1β injections in young mice can recapitulate aspects of hematopoietic aging (19, 43). Another example is Ccl5 (RANTES) that is enriched in the aged microenvironment (12). Exposure of young HSCs to Ccl5 induced the same myeloid bias observed in aged HSCs. Interestingly, in *Ccl5* knockout (KO) mice there was an increase in lymphocytes, suggesting that Ccl5 is required for steady-state balance of lymphoid and myeloid lineages. As evidence that the microenvironment has the potential to ameliorate aged HSCs, transplant of aged HSCs into *Ccl5* KO recipients helped balance lineage output, with significantly fewer myeloid and more B cells being produced. Mechanistically, Ccl5 activates the mTOR pathway that has a critical role in the aging process.

The development of single cell RNA-Seq (scRNA-seq) technology has provided a comprehensive view of all immune cell types during aging, validating and further expanding our perspective on aged immunity (2). Since most of these studies were performed on immune cells harvested from peripheral tissues instead of BM, how the microenvironment impacts immunity during aging remains largely unknown.

Diminished phagocytosis by macrophages, neutrophils, and dendritic cells, and their reduced efferocytosis to engulf apoptotic cells, have been described in aged mice and humans (44–46). Consistent with the increased proportion of my-HSCs during aging, there is a gradual expansion of circulating myeloid cell populations, mainly monocytes and neutrophils, relative to lymphoid cell populations. Although significant changes occur in tissue-resident macrophages during aging, analysis of circulating monocytes (i.e., macrophage precursors) reveals an expansion of non-classical monocytes without significant transcriptomic alterations in young vs old healthy humans (2). By contrast,

changes in short-lived neutrophils are observed in aged mouse BM, with significant expansion of the IL-1β-expressing subset of neutrophils (47, 48), suggesting a role for the aged BM microenvironment in age-associated neutrophil dysregulation. The expansion of pro-inflammatory aged neutrophils can be ameliorated by systemic dietary intervention, such as NAD(+) augmentation with nicotinamide riboside (49), providing a metabolic preventative approach.

The age-associated decrease in lymphopoiesis is primarily reflected in a reduced B cell compartment. Despite their decreased number, a progressive increase in B cell clonality is seen in aging mice, which is attributed to a cluster of plasma B cells (50). In addition, the aged B cell compartment shows altered B cell composition and function, such as increased incidence of monoclonal gammopathy of undetermined significance in mice and humans that has been associated with pre-malignant multiple myeloma (51), and expansion of "age-associated B cells" in mice (52, 53). These age-associated B cells are distinct from the conventional naïve and memory B cells and are thought to arise in response to damage-associated molecular patterns, such as debris and chromatin from apoptotic cells, via the TLR7/TLR9 axis. These age-associated B cells secret IL-4 and IL-10 on activation (52), further contributing to inflammaging.

As essential players in anti-infection and anti-cancer immunity, T cells, including both CD4+ and CD8+ T cells, undergo aging-associated changes in both mice and humans (2). It was proposed that T cell aging is represented by two-tier molecular hallmarks (54). The primary hallmarks include thymic involution, mitochondrial dysfunction, profound genetic and epigenetic alterations, and loss of proteostasis. The secondary hallmarks include reduction of the TCR repertoire, naïve-memory imbalance, T cell senescence, and lack of effector plasticity. Together, these age-associated changes in T cells lead to immunodeficiency and inflammaging. Therefore, the aged adaptive immune system is characterized by T cell dysfunction that is responsible for elevated susceptibility to infection and cancer, as well as increased autoimmunity. Recent evidence indicates that age-associated intrinsic alterations in CD4+ T cells are sufficient to reduce humoral responses in young mice (55) and accelerate organism-wide aging phenotypes (56, 57). Since T cell development and mature T cells mainly stay outside the BM, it is conceivable that the impact of an aged BM microenvironment may be limited to BM-resident T cells. In addition to their contribution to inflammaging, BM-resident CD4+ Treg cells promote the survival and clonal advantage of aged HSCs through MHC II engagement and Connexin 43-mediated transfer of cAMP (58).

In summary, aged hematopoietic cells contribute significantly to increased BM inflammation, which in turn further exacerbates hematopoietic dysfunction.

Bone marrow endothelial cells

The BM vasculature is heterogeneous, with vessels that vary in both function and location, and there has been ongoing debate about the primary niche for HSCs in the BM (59). In broad terms, these are classified as endosteal capillaries and central marrow sinusoids, with both regions having been considered as the true home of HSCs (20, 60–62). More specifically, small capillaries in endosteal regions of the metaphysis and trabecular bone of the diaphysis, called transition zone vessels (TZVs) (61), or Type H capillaries ($CD31^{High}$, $Emcn^{+}$ (63)), connect to arterioles and are surrounded by osteoprogenitors (61, 63, 64). Sinusoids or Type L vessels ($CD31^{Low}$, $Emcn^{+}$ (63)), are broad and fenestrated, found throughout the BM, and facilitate trafficking of hematopoietic cells into and out of the circulation (65).

The changes that occur in BMECs during aging are still being resolved, with different research groups presenting multiple views (Figure 1). Some have observed that endosteal ECs, like arterioles and TZVs, are reduced during aging, but overall EC volume and area occupancy are unchanged, leading to the conclusion that BM sinusoids are preserved upon aging (15). Other studies also found ECs near the endosteum of aged BM were reduced and central marrow sinusoids were unchanged, although small capillaries throughout the BM are increased (16, 18). In contrast to these studies, Wu et al. recently showed that BM sinusoids are more abundant in aged BM, and the number of arterioles is unchanged (20). In a study of middle-aged female mice, histological analysis of bones showed no change in the number of sinusoids and arterioles, however, fluorescence-activated cell sorting (FACS), followed by scRNA-seq and analysis, showed a slightly higher percentage of arterioles and lower percentage of sinusoids (66). It has been difficult to reliably quantify aged BMECs and mesenchymal stromal cells (MSCs) by FACS, presumably because the cells become more fragile (13, 19, 21, 66, 67). These studies have used different protocols, types of bones, imaging techniques, and FACS to quantify niche cells in the aged BM, and these methods must be comprehensively compared before a consensus can be reached. Ultimately, it must be determined if and how the changing proportions and spatial distribution of BMECs during aging directly impacts HSC function.

Importantly, it may be functional changes and the supportive capacity of aged BMECs, such as cytokine production, that is more relevant than cell number or spatial relationships between HSCs and niche cell types. The reduced function of vasculature during aging has been well-described and reviewed elsewhere (68). Aged blood vessels become dilated, leaky, and have overall poor function. Reduced vascular endothelial growth factor (VEGF) signaling during aging, and associated capillary loss, may underlie the aging phenotype in many organ systems (69). Aged ECs have significantly lower levels of KITLG (aka SCF) and CXCL12 (aka SDF-1) (13, 18, 70). The AKT/mTOR axis specifically in ECs is required for maintaining HSC function (71). While mTOR inhibition is widely accepted as rejuvenating and promoting longevity (72), in BMECs reducing mTOR signaling negatively impacts HSC function (71). Aged ECs are sufficient to induce aging phenotypes in young HSCs (13), and similarly, chronic activation of inflammatory pathways in BMECs of young mice recreates the aging-associated myeloid-biased differentiation of HSCs (73). Blocking activated inflammatory pathways in BMECs can rescue HSC function (73),

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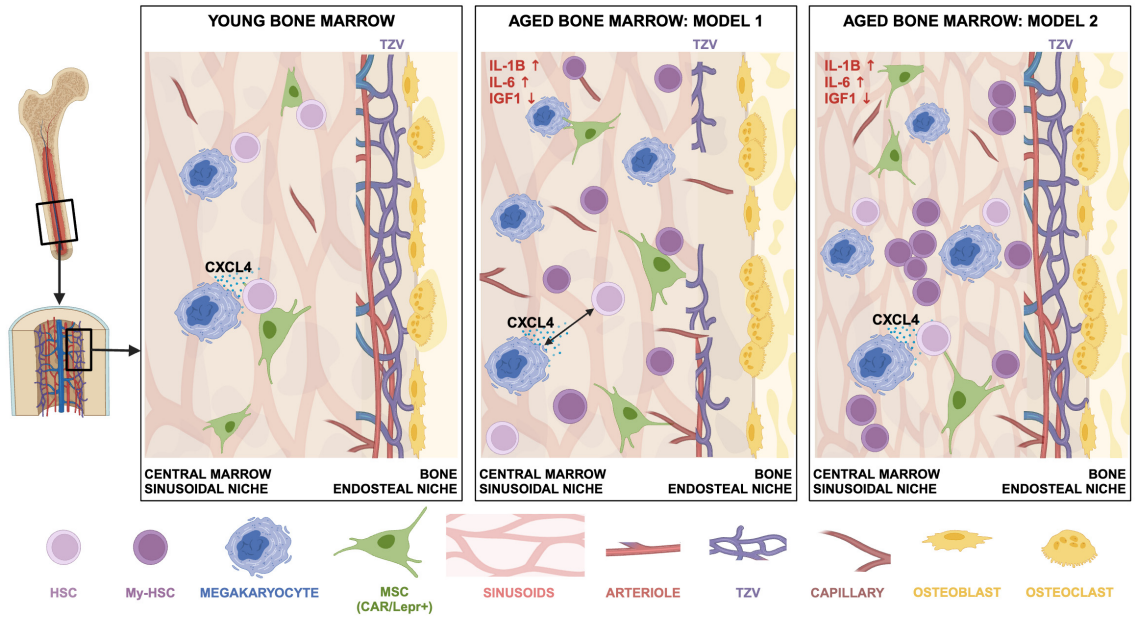

FIGURE 1
Different views of the changing bone marrow microenvironment during aging. Sinusoidal vessels and MSCs (CXCL12-abundant reticular (CAR)/Lepr+ cells) are abundant throughout the BM and are therefore always close to an HSC. Megakaryocytes promote HSC quiescence by producing CXCL4 (25). There is a consensus that during aging: 1) HSC and megakaryocyte numbers increase; 2) there is an increase in myeloid-biased HSCs (My-HSC); 3) inflammatory cytokines increase (e.g., IL-1β and IL-6), and IGF1 levels decrease; 4) osteoclasts increase and osteoblasts decrease, contributing to bone loss. Aged BM Model 1: The endosteal niche is compromised, with decreased numbers of TZVs and arterioles; it follows there are fewer HSCs near the endosteum. Sinusoids are largely unchanged in the central marrow, but capillaries are increased. There is greater distance between HSCs and megakaryocytes (15–19). Aged BM Model 2: The endosteal niche is intact and there is no change in arteriole numbers. Sinusoids in the central marrow are more abundant and shorter. There is no change in distances between HSCs and the endosteum, sinusoids, arterioles, or megakaryocytes. HSCs and progenitors tend to cluster closer together (20). Not shown: For clarity, many cell types, such as myeloid cells, have been excluded. Nestin-GFP+ MSCs, other MSC subtypes, and TH+ sympathetic nerve fibers are not shown because a consensus has not been reached on the abundance of these cell types during aging. Created in BioRender. Tamplin, O (2025). https://BioRender.com/l27j847.

and likewise, young ECs have the capacity to restore some function in aged HSCs (13). Interestingly, young ECs can provide radioprotection for transplant recipients when co-infused with HSCs (13). Activation of Notch signaling in aged BMECs can restore some of the HSC support function, as the number of arterioles, capillaries, and phenotypic HSCs increased, but the number of functional HSCs did not increase, as determined by limiting dilution transplantation (18). Together, these findings suggest there is therapeutic potential in rejuvenating the aged niche to restore HSC function during aging.

Age-related neural alterations and their impact on HSC aging

The bone marrow receives a generous supply of nerves that enter the cavity with the vasculature that carry nutrients into the BM. Imaging and tracing studies revealed that the BM is largely comprised of sympathetic and sensory nerve fibers (17, 74–76). Many nerve fibers in the BM are tightly associated with arterioles, with very few nerve terminals located in the hematopoietic parenchyma and sinus walls. Sympathetic nerves are known to regulate various functions of HSCs at steady state and disease progression mainly via stromal cells, mediated by neurotransmitter noradrenaline binding to adrenergic receptors (17, 75–77). A recent study revealed that nociceptive nerves regulate HSC mobilization via the secretion of calcitonin gene-related peptide (CGRP) that acts directly on HSCs via CGRP receptor (74).

Neuropathy is common in elderly people. Consistent with this notion, one study revealed a significant reduction of bone marrow sympathetic innervation in old compared to young femurs (17). This study also indicated that surgical denervation or deletion of *Adrb3* in young mice induces dramatic remodeling of the HSC niche and leads to premature aging-like changes in HSCs. Notably, they showed that supplementation of an ADRβ3 agonist, BRL37344, in old mice significantly rejuvenates the *in vivo* function of aged HSCs. This study highlights a potential novel approach for niche-targeted stem cell rejuvenation therapy. Similarly, neuropathy is also found in a mouse model of an aged-related blood disease, myeloproliferative neoplasm (MPN), induced by a mutant form of Janus kinase 2 (JAK2V617F) (77). Treatment with the same ADRβ3 agonist BRL37344 blocks myeloid expansion and disease progression. However, studies regarding the neural alterations with age and their contributions to HSC aging remain controversial. A conflicting study using whole-mount imaging of skulls and thick tibial sections did not find reduced sympathetic nerve fibers in the aged BM, and instead actually found increased

sympathetic innervation (78). Whether these discrepancies result from the use of different bones and methodologies will require further investigation. In the latter study, they found that increased bone marrow adrenergic innervation promotes myeloid expansion through activating ADRβ2 (16). Interestingly, this study revealed that ADRβ3 exhibits opposite regulation of myelopoiesis as compared with ADRβ2. Lack of ADRβ3 accelerates HSC aging, and chronic treatment with an ADRβ3 agonist BRL37344 reduces HSC expansion and restores their myeloid skewing. The situation is further complicated by a phase II clinical trial that treated *JAK2*-V617F-positive patients with the sympathomimetic agonist mirabegron that yielded a slight overall hematologic improvement in a subset of patients, but didn't reduce the *JAK2*-V617F allele burden (79). This raised the possibility that modulation of only one adrenergic signaling pathway is insufficient, and other alternative mechanisms may compensate. Further studies of other adrenergic signaling pathways are needed to clarify the neural contributions to the bone marrow niche and HSCs with age.

Perivascular mesenchymal stromal cells

BM perivascular MSCs wrap around the blood vessels and represent an important cellular component in the HSC niche. MSCs have the potential to self-renew and differentiate into bone, fat and cartilage, and are highly enriched in niche factor expression, such as CXCL12 and SCF. However, BM MSCs are a very heterogenous cell population (80, 81), and it remains unresolved how the overall number of MSCs changes during aging. Some studies suggested a decline in MSC number in old individuals (82, 83), or no significant changes (84, 85), whereas other studies revealed an increase and/or decrease in different subsets of MSCs (17, 19). These discrepancies may be explained by different markers used to define MSCs, or different processing methodologies. However, despite these differences, common functional dysregulation of aged MSCs has been described. Importantly, when aged skeletal stem cell-derived stroma (i.e., bone, cartilage, and mesenchymal lineages, but not fat) is used for co-culture with young HSCs, it has the effect of producing age-related myeloid skewing of hematopoietic output (86, 87).

First, MSCs form colony-forming unit-fibroblasts (CFU-F) *in vitro*, and aged MSCs showed reduced CFU-F activity and reduced expression of HSC niche factors, including CXCL12, SCF, and ANGPT1. IGF1 produced by MSCs declines during aging and has a significant contribution to the HSC aging phenotype (11, 66). This dysregulation of aged MSCs could be rejuvenated by activating adrenergic signaling. Another common feature of MSCs from old individuals is their reduced osteoblast differentiation and increased bias toward adipocyte differentiation, with old bones showing an increase in the adipogenic marker PPARγ (88, 89). In old mice the adipogenic potential of Sca-1$^+$ MSCs was unchanged but the osteogenic potential of Sca-1$^-$ MSCs was reduced (88). Loss of trabecular bone was also observed in old bones. Accumulation of marrow adipose tissue (MAT) was pronounced in old mice after being fed a high fat diet. Importantly, accumulation of adipocytes in the bone marrow contributes to age-related impairment of hematopoiesis. This age-related adipogenic skewing contributes to loss of osteoblasts, and increased BM adiposity, leading to a change in overall BM cellularity and bone density. The balance between adipo-osteogenic differentiation is regulated by critical signaling pathways (Extracellular matrix-Integrin, Wnt, Notch, BMP, Hedgehogs, and FGFs) and key transcription factors, such as PPARγ and C/EBPs for adipogenesis, and Runx2 and Osterix for osteogenesis (90). Recent studies also revealed microRNAs, circular and long RNAs as additional regulators in controlling the adipo-osteogenic balance (91–93). Adipocytes were considered to be negative regulators of hematopoiesis (94), however, growing evidence suggests they are involved in HSC regeneration (95, 96). Adipocytes are much less abundant in mouse bones compared to human bones that have increased adiposity during aging that correlates with increased adjacent myeloid cells and CD34+ stem and progenitor cells (97). An accumulation of osteoclasts from macrophages was observed with aging. The disruption of the balance between bone-forming osteoblast and bone-resorbing osteoclast leads to an imbalance in bone remodeling and often contributes to bone loss associated with osteoporosis (98). This is consistent with age- and menopause-induced bone loss seen in clinic (99).

Aging is characterized by increased inflammation, which is accompanied by cellular senescence. Consistent with other aging tissues, there is a strong inflammatory signature that emerges in MSCs and the aging stroma (16, 100). The stroma of middle-aged telomerase knockout mice (*Terc*$^{-/-}$) had a dramatic increase in G-CSF levels and was less able to support HSCs (101). Recent studies have identified bone marrow stromal cells as sensors of age-associated changes and as a source of IL-1β to drive the proinflammatory nature of the bone marrow niche and HSC aging (19). These studies showed that blocking IL-1 signaling could rejuvenate hematopoietic aging and indicated that targeting IL-1 is a novel strategy to improve blood production during aging. The accumulation of BM adipocytes and increased fatty bone marrow and inflammatory signals during aging, specifically IL-6, can promote clonal hematopoiesis (102). Some studies found that BM MSCs underwent senescence *in vitro* along with aging, including increased DNA damage response and upregulation of senescence associated genes, p16(INK4a), p53, and p21. However, further studies are needed to investigate the senescence-associated phenotypes in bone marrow MSCs *in vivo*.

Sex-related differences

There are clear sex-related differences in hematopoiesis during aging (103–106). Our understanding of this has been complicated because studies have used, for example, only males (107), only females (66), or males and females (108). Sex-related differences in hormone levels, such as estrogen, increase HSC proliferation in

females (109). Follicle-stimulating hormone (FSH) is higher in middle-aged and old female mice (104). Sex-related differences have also been found between male and female MSCs, with females having a lower CFU-F capacity (110). Female mice were more responsive to VEGF alleviation of aging phenotypes than males (69). The changes in sex hormones that occur during aging contribute to adipocyte accumulation in the BM (111, 112). Interestingly, the increase in HSC number that is associated with aging occurs in middle age (60-70 weeks) for female mice and at old age (85-90 weeks) for males (104). Although these middle-aged female mice had the aging hallmark of increased HSC frequency, they did not have the inflammatory signatures of old mice. These data suggest mouse studies must be carefully designed to consider if males and females will be grouped together, and how middle aged versus old will be defined. These factors could add to the already high degree of variability associated with aging phenotypes that may be partially resolved with larger sample sizes. To gain a more consistent understanding of changes in hematopoiesis across the lifespan of mouse models, not only the precise age, type of bone, and experimental methods must be considered, but also the sex.

Discussion

A barrier to progress in this field is, of course, the time and cost required to age different mutants and transgenic lines. Although there are colonies of aged wild-type mice that are available to researchers, a shift in focus to middle-aged mice will make aging studies more accessible, as the wait time to reach study age could be reduced by 6 months (66).

There is ongoing debate about the importance of HSC location and distance between niche cells in the microenvironment (59). This is further complicated by the changes observed in both HSC and niche cell populations over the lifespan. An alternative perspective is that the spatial relationships between HSCs and niche cells may not be the most significant factor that impacts HSC regulation and function. Stated another way, perhaps the changes in distance between HSCs and niche cells during aging, at least those that do not require direct contact, such as Notch and Integrin, do not translate into functional changes. For example, during embryonic development, the effect of SHH and BMP morphogen gradients during patterning of the neural tube can extend up to ~100 microns, or many cell diameters (113).

There are also additional layers of spatial information present in the BM microenvironment, such as local oxygen tension and metabolites that are higher near the endosteum (114, 115). Furthermore, significant systemic changes are measurable in the BM fluid during aging that broadly indicate an inflammatory state (19, 66). Parabiosis has shown young blood-borne factors can rejuvenate old mice, just as old blood can accelerate aging of young mice (116). These studies show the exciting potential to reverse some of the effects of aging in HSCs and the BM microenvironment.

Author contributions

XG: Writing – original draft, Writing – review & editing. JZ: Writing – original draft, Writing – review & editing. OJT: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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