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## Concise Review: Hematopoietic Stem Cell Aging, Life Span, and Transplantation

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**Key Words.** Aging • Hematopoietic stem cells • Stem cell transplantation • Gene therapy

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### ABSTRACT

Self-renewal and multilineage differentiation of stem cells are keys to the lifelong homeostatic maintenance of tissues and organs. Hematopoietic aging, characterized by immunosenescence, proinflammation, and anemia, is attributed to age-associated changes in the number and function of hematopoietic stem cells (HSCs) and their microenvironmental niche. Genetic variants and factors regulating stem cell aging are correlatively or causatively associated with overall organismal aging and longevity. Translational use of HSCs for transplantation and gene therapy demands effective methods for stem cell expansion. Targeting the molecular pathways involved in HSC self-renewal, proliferation, and homing has led to enhanced expansion and engraftment of stem cells upon transplantation. HSC transplantation is less effective in elderly people, even though this is the demographic with the greatest need for this form of treatment. Thus, understanding the biological changes in the aging of stem cells as well as local and systematic environments will improve the efficacy of aged stem cells for regenerative medicine and ultimately facilitate improved health and life spans. *STEM CELLS TRANSLATIONAL MEDICINE* 2012;1:651–657

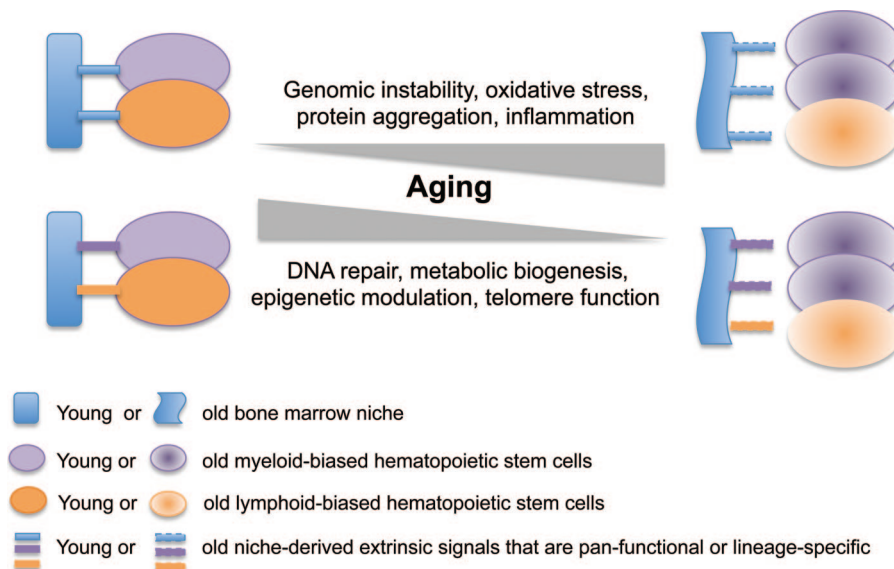
### STEM CELL AGING

Stem cells are key to the homeostatic maintenance of mature and functional tissues and organs. They self-renew and produce progeny to replenish dying or damaged cells throughout an organism's lifetime. Because of these unique characteristics, stem cells are traditionally thought to be immortal and exempt from aging. However, a reduced ability to repair tissues and an increased susceptibility to cancer during aging indicates that stem cells may undergo an age-related functional decline. Because of the unprecedented experimental model systems that are available for the exploration of hematopoietic stem cells (HSCs), stem cell behavior in aged versus younger populations in mice and humans has been extensively investigated. Thus, HSC aging has served as an ideal model for studying the interplay of stem cells, aging, and age-related diseases. It is likely that the same broad concepts that define and characterize blood-forming stem cells would apply to other types of stem cells [1]. A clear understanding of stem cell regulation in the aging process could provide important information for the efficient use of stem cells for treating age-associated diseases.

### AGING OF THE HEMATOPOIETIC SYSTEM

At the apex of the hematopoietic hierarchy, HSCs are responsible for lifelong production of

all types of blood cells. The functional capacity and quantity of blood cells change dramatically with age, and immune deficiency and anemia are considered major contributory factors to the increased morbidity and mortality in aged populations [2]. Immune responses are induced by coordination of adaptive and innate immune systems, which involve lymphoid (B, T lymphocytes) and myeloid leukocytes, respectively. As age advances, a dramatic decline in the production of naïve T cells is apparent as well as an accumulation and clonal expansion of memory and effector T cells leading to decreased immune defense and increased autoimmunity among the elderly [3]. The number of B cells decreases with age, and old B cells generate antibodies with less affinity and diversity [4]. In contrast to the lymphoid lineage, myeloid compartments are expanded with aging, which provides a proinflammatory environment in the body, becoming detrimental later in life [5]. Furthermore, other types of immune cells, such as natural killers and dendritic antigen-presenting cells, have been shown to diminish and functionally deteriorate with old age [6, 7]. These “immunosenescence” and “inflammaging” phenotypes are implicated in many pathologically significant health problems in aged populations, such as cancer, autoimmune diseases, and chronic inflammatory disorders.



**Figure 1.** Aging of the hematopoietic stem cells and their niche. Hematopoietic stem cells (HSCs) and their bone marrow microenvironmental niche undergo age-related changes because of a burden of genomic damage, telomere dysfunction, metabolic byproducts, and epigenetic shift during the aging process. At a young age, the composition of the HSC compartment, including myeloid-biased (My-bi) and lymphoid-biased (Ly-bi) HSC subpopulations, and their differentiation capacity are homeostatically maintained, enabling a balanced production of blood cells. In the old bone marrow, the HSC pool is expanded and My-bi HSCs become dominant over the Ly-bi population, resulting in a myeloid skewing at the expense of lymphocytes. Aging of the niche results in decreased homing and enhanced mobilization of old HSCs, thus demonstrating a reduced capacity to support HSC engraftment and differentiation in HSC transplantation. Note: analysis of the aging literature suggests that ages older than 60–65 are commonly called “the older population” [8–10, 67, 68, 82], even though “age” should be defined by the functional analysis and there is no general agreement on the definitive cutoff for “old age” [22].

### HSC AGING AT THE POPULATION LEVEL

HSCs are the foundation of the blood system, and aging phenotypes in peripheral blood cells could be caused by a decline in HSC numbers in old age. However, the relationship is clearly not that simple. The evidence that the number of human or mouse HSCs declines sufficiently in old age to threaten adequate blood cell production is not compelling. Instead, recent studies in aging of human HSCs show that the proportion of immunophenotypically defined hematopoietic stem/progenitor cells, either CD34+CD38– or more primitive Lin–CD34+CD38–CD90+CD45RA– cells, increases in the bone marrow of elderly individuals (>65 years) [8, 9]. In contrast, the frequency of lymphoid progenitor cells dramatically decreases with age, which accounts for lymphoid deficiency in the elderly [8]. Although the myeloid progenitor population was found to persist at the same level in the bone marrow during aging, its relative composition in blood cells is indeed increased, which may explain age-associated myeloid skewing [9]. A very recent study identified CD49f as a novel marker for specifying more primitive HSCs in humans [10]. By adding CD49f-positive selection on Lin–CD34+CD38–CD90+CD45RA– cells, HSCs from human cord blood can be further enriched by approximately twofold. It will be of interest to determine whether this newly refined HSC population also demonstrates age-associated expansion. In mouse HSC aging, we and others identified changes similar to those in humans, such as an increased HSC number and myeloid skewing and lymphoid deficiency in old mice, despite a large strain-specific difference in the maintenance of the HSC population during aging [11–17].

Two models are proposed for HSC aging at a population level: (a) a clonal alteration model, and (b) a population shift model [18]. The clonal alteration model emphasizes uniform change of

HSCs with aging as a homogeneous population, among which an individual aged stem cell differentiates toward the myeloid lineage at the expense of the lymphoid lineage. Recently, accumulating evidence from several laboratories has suggested a population shift model of HSC aging, which implies that HSCs are heterogeneous and age-related hematopoietic phenotypes are derived from a changing composition of distinct classes of HSCs [17, 19–22] (Fig. 1). Within the HSC compartment in mice, three classes of HSCs are evident: balanced, lymphoid-biased (Ly-bi), and myeloid-biased (My-bi) stem cells. All three subsets of HSCs exist in both young and old marrows, but the composition shifts with aging such that the My-bi HSC subpopulation is selectively expanded and becomes dominant in old marrow. In humans, characterization of bone marrow HSCs and their age-associated changes has lagged behind, largely because of insufficient information for markers that distinguish subsets of HSCs. However, clinical trials of stem cell gene therapy provide a unique opportunity for probing the model of HSC clonal diversity in humans [23]. In this therapy, mutated genes in HSCs are corrected by viral vector-mediated genetic replacement, and gene-modified HSCs are transplanted into patients. The lineage reconstitution of injected stem cells is evaluated by vector integration sites (ISs) in the genome. Several studies show that ISs are present only in lymphoid cells, supporting the existence of lineage-biased stem cells in humans. In contrast, others find that patients’ myeloid and lymphoid cells share common ISs, an observation in favor of nonbiased hematopoiesis [23]. Thus, organization of the HSC hierarchy in humans and how it changes with age remain largely elusive. Solving these puzzles will help with selection of the optimal stem cell population for gene modification to enhance the effectiveness of stem cell gene therapy [24].

### HSC AGING AT THE CELLULAR LEVEL

Aging is accompanied by accumulation of genomic damage, telomere shortening, and a burden of metabolic byproducts. All these cellular changes activate multiple signaling pathways that are involved in apoptosis, senescence, or impaired proliferation, ultimately resulting in a functional decline of aged stem cells [25–28]. HSCs from old mice have a decreased ability to reconstitute myeloablated recipient mice [11], are less efficient at homing to and engrafting in the bone marrow of recipients [29], and are more easily mobilized into peripheral blood [30]. Aged HSCs are more actively cycling [11], although this appears to be inconsistent with the report that the proliferative response of HSCs to the early-acting cytokines c-kit ligand (KL), flt3 ligand (FL), and thrombopoietin (TPO) decreases with age [15]. In humans, proliferative properties of HSCs from bone marrow of aged people (>65 years old) are significantly higher than those from young people (ages 20–30) [8, 9]. Elderly human HSCs xenotransplanted into immunodeficient mice do not engraft or generate lymphoid progeny as efficiently as young cells [8], although another study has shown that aging does not affect the repopulating capacity of human HSCs [9]. The reason for this inconsistency may be that transplanted cells are not the same because of different stem cell markers used in two studies (Lin<sup>−</sup>CD34<sup>+</sup>CD38<sup>−</sup>CD90<sup>+</sup>CD45RA<sup>−</sup> vs. CD34<sup>+</sup>CD38<sup>−</sup>). Again, these studies emphasize the importance of improving methods for isolation of “true” HSCs and distinguishing them from downstream human hematopoietic progenitors.

### HSC AGING AT THE MOLECULAR LEVEL

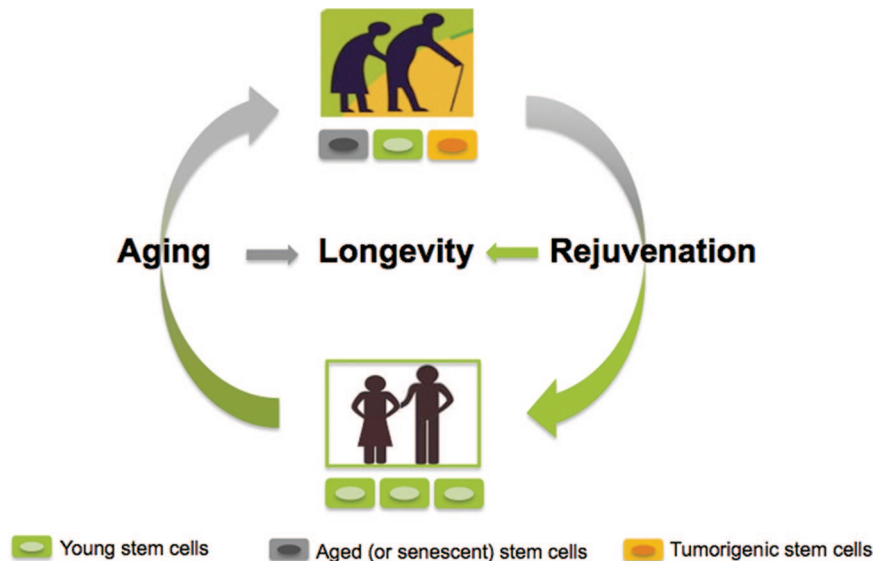
Deciphering molecular events regulating self-renewal and multipotency in stem cell aging is a major challenge in the field of aging research. Microarray analysis comparing profiles of young versus old HSCs reveals a general aging signature of HSCs at the expression level. In both human and mouse, expression of genes linked to oxidative stress, protein aggregation, and inflammatory responses increases with age, whereas genes involved in genomic integrity (DNA repair and chromatin remodeling) and transcriptional regulation are age-repressed [8, 31–33]. In addition, upregulation of myeloid genes and downregulation of lymphoid genes are found in old HSCs, suggesting that age-related lineage skewing is partly a consequence of transcriptional changes. A recent study by Wang et al. has identified a novel DNA damage checkpoint, Batf, and its role in regulating HSC functions [34]. DNA damage induced by irradiation and telomere dysfunction elevates Batf expression, leading to restriction of self-renewal and induction of differentiation in stem cells. Age-associated accumulation of DNA damage occurs in both My-bi and Ly-bi HSCs. However, My-bi HSCs appear more resistant to DNA-damage-induced differentiation and depletion than Ly-bi HSCs, perhaps because Batf is less abundant in My-bi cells. Thus, differential expression of Batf in lineage-biased HSCs could be a molecular checkpoint for the predominance of My-bi HSCs and increased incidence of myeloid malignancy in elderly people. A new insight into molecular regulation of HSC aging has been revealed by linking intracellular activity of small RhoGTPase Cdc42 to the decreased HSC functionality with aging [35]. Florian et al. found that intrinsic Cdc42 activity in HSCs increases with natural aging and that enforced activation of Cdc42 in genetically modified HSCs leads to a premature hematopoietic aging phenotype [35].

More interestingly, Cdc42 distribution in the cytoplasm is polarized in young HSCs but diffusely distributed in aged ones. Pharmacological inhibition of Cdc42 in aged stem cells not only restores their polarity but also rejuvenates them to a youthful state.

Epigenetics is emerging as a particularly intriguing new frontier for HSC aging research [36]. Epigenetic modifications, most commonly in methylation status changes of DNA and biochemical modifications of core histones, have been shown to accumulate with age and lead to the cumulative loss of gene regulation over time [37]. Although little is known about the epigenome of old HSCs, several studies have highlighted the important role of DNA methylation and histone modification in regulating young HSCs. Conditional deletion of DNA methyltransferases causes defects in stem cells regarding self-renewal, retention in bone marrow niches, and myeloid cell production [38, 39]. Histone proteins (H2a.x and its family members H2a.z and H3) are the key modifiers of chromatin regions important for transcriptional regulation of genes that are implicated in stem cell proliferation and lineage differentiation [40–42]. Moreover, development of high-throughput sequencing techniques has facilitated the characterization of an HSC-specific methylome that is distinct from mature blood cells in both human and mouse [43–45]. However, none of these studies were carried out in the context of aging. It will be interesting to investigate how these epigenetic factors regulate stem cell aging and how age-related changes in transcriptome are linked to those in the epigenome of HSCs.

### AGING OF THE HEMATOPOIETIC STEM CELL NICHE

A majority of adult HSCs reside in a discrete niche in the bone marrow composed of a collection of specific cells and extracellular matrix proteins that provides a nurturing microenvironment. HSC activity depends on both intrinsic properties of the cell and extrinsic signals from niche [46]. The precise mechanism of the interplay of HSCs with their local environment, especially in the aging process, is largely unknown. However, it is certain that decreased bone formation, loss of bone mass, and accumulation of fat in the marrow become more pronounced with advancing age, leading to the altered composition of cell types and extracellular matrix in the niche. The candidate niche cells include osteoblasts [47], Cxcl12-abundant reticular cells [48], nestin-positive mesenchymal stem cells [49], Schwann cells [50], and perivascular cells [51], which constitute the endosteal and vascular regions of niche. It has been shown that aging causes a decrease in the number of mesenchymal stem cells and a skewing of their differentiation toward adipocytes in the old marrow of both mouse and human [52, 53]. Transforming growth factor- $\beta$  is an important regulator of HSC quiescence and self-renewal [50, 54], whose presence in the niche decreases with age [53]. Age-associated telomere shortening leads to abnormal cytokine production and functional decline in niche mesenchymal progenitor cells, resulting in a reduced capacity of the aged microenvironment to support HSC engraftment and differentiation [55]. Thus, aging has a potential to compromise the cross-talk between stem cells and supportive niches, thus contributing to HSC aging. Two possible models are proposed for the effects of niche on HSC aging (Fig. 1): (a) signals from niche cells uniformly regulate lineage-biased HSC populations during aging (Fig. 1, top); and (b) distinct signals from niche cells dictate the development of different lineage-biased HSC subsets and, with aging,



**Figure 2.** Effects of stem cell aging and rejuvenation on organismal longevity. During organismal aging, stem cells may undergo senescence or apoptosis, they may become tumorigenic, or they may retain their “youthful” state. Age-associated changes in the stem cell population underlie the increased disease incidence and decreased regenerative capacity in elderly people and ultimately produce negative effects on organismal longevity. In order to counteract such deleterious effects, stem cell-based gene therapy and regenerative medicine hold great promise in treating age-related degenerative and malignant diseases. These therapeutic strategies will, hopefully sooner rather than later, improve health span and life span in humans.

cause selective expansion or loss of specific HSC lineages (Fig. 1, bottom).

#### HEMATOPOIETIC STEM CELL AGING AND ORGANISMAL LIFE SPAN

Accumulated multiorgan changes with aging limit longevity. There are two general theories of organismal aging and longevity: (a) antagonistic pleiotropy, and (b) damage-based. The former postulates that evolution selects a genetic composition that confers overall higher survival and/or fecundity. Genes that are beneficial early in life are conserved, although they may be detrimental in late life; thus, they are pleiotropic and their resulting effects are antagonistic. Cellular senescence is proposed to be an example of antagonistic pleiotropy given that it prevents cancer during early life, whereas later in life it contributes to decreased regenerative capacity of tissues [56]. The damage theory emphasizes that aging is caused by accumulated cellular damage over a lifetime, such as via reactive oxygen species, cross-linked proteins, free radicals, and genetic mutations [57, 58]. Aging is a complex process that affects every cell in the body. As long-lived cells, stem cells are exposed to both intrinsic and extrinsic assault over their lifetime. Thus, it has been hypothesized that aging or functional failure of tissue-specific stem cells may limit tissue repair and renewal, thereby contributing to overall organismal aging and life span reduction [57].

A recent finding concerning the novel function of *PGC-1* transcriptional regulators provides direct evidence for the interrelationship between stem cell aging and longevity in *Drosophila* [59]. Overexpression of *PGC-1* in intestinal stem/progenitor cells delays the onset of aging-related changes and improves homeostasis in the intestine, leading to an extended life span. The underlying cellular mechanisms are enhanced mitochondrial biogenesis and energy metabolism. Interestingly, *PGC-1* is regulated by *Lkb1*, which is an evolutionarily conserved regulator of cellular energy metabolism. *Lkb1* was recently found to be critical for the survival of HSCs in mice. Loss of *Lkb1* leads to the impairment of

HSC self-renewal and quiescence and thus to exhaustion of the HSC pool. *Lkb1* knockout mice demonstrate high prenatal lethality and a shorter life span because of severe blood cytopenia [60–62]. Thus, the effect of *Lkb1* on organismal longevity is through the regulation of metabolic homeostasis in stem cells.

Genetic variants play a critical and complex role in conferring exceptional longevity. However, it is difficult to probe these variants and their combined effect on longevity through classic modification (knockout or knockin) of genes of interest in animal models. Thus, a surrogate system using a variety of inbred mouse strains aids in revealing these longevity-associated variants. Inbred mouse strains demonstrate wide natural variation in life span and quantitative phenotypes in the HSC population. Using quantitative trait loci mapping, we and others identified several murine loci tightly linking age-associated changes in the number and proliferation of hematopoietic stem/progenitor cells to life span [63–65]. These results reinforce the notions that stem cell dynamics during aging may have an effect on longevity and that the same gene(s) may regulate both traits. Although much research remains to be done to identify the underlying gene(s) and its mode of action, given these correlative data, we have postulated that adult stem cells, especially blood-forming tissues but perhaps more generally those in a variety of organs, collectively affect longevity by influencing the replacement of organ-specific effector cells. Continuous replacement of short-lived blood cells, including immune system cells, not only is a prerequisite for life but is directly dependent on the function of stem and progenitor cells (Fig. 2).

#### AGING AND HSC TRANSPLANTATION

Because of the extensive regenerative capacity of stem cells, stem cell-based gene therapy and tissue regeneration hold considerable promise for treating a range of serious diseases [66]. Among all stem cell-based therapies, hematopoietic stem cell transplantation (HSCT) is the only one with a well-established

clinical regimen, and it remains an effective approach for patients with certain hematological diseases. HSCT involves the intravenous infusion of autologous (patient's own cells) or allogeneic (from related or unrelated donors) stem cells collected from bone marrow, mobilized peripheral blood, or umbilical cord blood to the patients. Current clinical and experimental HSCTs face two obstacles that limit the success of this treatment: insufficient numbers of transplantable stem cells and low engraftment efficiency. These limitations are exacerbated by advancing age [67]. The National Marrow Donor Program has reported that donor age is the only factor significantly associated with overall survival rate of HSCT recipients: the younger the donor, the better the long-term outcome [68].

Why is HSCT less effective in old patients? One stem cell-intrinsic limit is the telomere length. It has been shown that telomeres in stem/progenitor cells from human umbilical cord blood are longer than those from adult bone marrow. Telomere loss in hematopoietic cells is rapid within the first year of life, continues to decline until 50–60 years of age, and then is exaggerated beyond age of 70 [69]. Following HSCT, the telomere lengths of engrafted donor cells are shorter than those preceding transplant, probably because of the extensive replicative stress on engrafted cells [70]. In one report of clinical HSCT, a 7-year-old boy with acute lymphocytic leukemia was transplanted with marrow cells from a 61-year-old donor [71]. Despite successful engraftment, the patient experienced poor marrow function 2 years post-transplant. The telomere lengths of donor cells recovered from the patient were significantly shorter than those of the original donor cells. Thus, telomere attrition in aged donor cells appears to correlate with poor graft function. Excessive production of reactive oxygen species and accumulation of DNA damage was also observed in hematopoietic stem/progenitor cells isolated from bone marrow of elderly healthy individuals (72–84 years) and HSCT patients [27]. Such damage significantly impairs the repopulating activity of the aged and engrafted stem cells. These scientific findings provide useful information for optimizing HSCT in the clinic in the following ways. (a) Age-related cellular changes, such as telomere length, may be a useful indicator of proliferative and engraftment potential following transplant. Pharmacological targeting of these events, such as preserving telomere length, could potentially lead to a more effective HSCT. (b) It may be necessary to limit the HSC donor pool to people younger than a defined age to ensure effective HSCT. (c) Cord blood-derived HSCs are a promising alternative source of cells for transplantation when a suitable autologous or allogeneic donor is not available. However, the number of HSCs recovered from a unit of cord blood is generally so low that it usually leads to the delayed engraftment and increased transplant complications [72].

The development of methods to expand HSCs that simultaneously permit maintenance of their self-renewal capability and of their engraftment efficiency is critical for the successful transplant. Ex vivo expansion of human cord blood CD34+ cells by immobilized Notch ligand Delta greatly expands the stem cell population and reduces the neutrophil engraftment time, and it has been evaluated with significant therapeutic value in an ongoing clinical trial [73]. In vitro expansion potential has also been described for the Wnt pathway participant prostaglandin E2 [74], soluble growth factor angiopoietin-like 5 (Angptl5), and pleiotrophin [75–77], and more recently for inhibition of the aryl hydrocarbon receptor by small molecule StemRegenin1 (SR1) [78] in xenotransplantation studies. A caveat for the expansion

ex vivo is that it may lead to the loss of long-term engrafting HSCs and perhaps graft failure. Rather than targeting HSC number, enhancing homing of stem cells to the niche by the inhibition of dipeptidylpeptidase IV (CD26) also improves the hematopoietic engraftment and reconstitution [79]. Since HSCs undergo dramatic changes with aging, it is not known whether the treatments described above will have similar effects on aged HSCs. For example, Notch signaling pathway becomes downregulated from fetal to adult stroma [80], indicating that Notch-mediated HSC expansion may not be as effective in adult stem cells as in cord blood. Thus, a better understanding of HSC aging will facilitate the development of treatment regimens that are more suitable for the older patients having HSCTs and other stem cell-mediated therapies.

There are multiple factors contributing to the inferior outcome of HSCT in older patients, such as the disease prognosis compared with younger patients, disease stage and type, and so forth [81]. Systemic and hormonal changes associated with aging, including changes in cytokine profiles to a more proinflammatory state, sex steroid changes, and other hormonal changes, also influence HSCT effectiveness [82]. Parathyroid hormone has been used in vivo to enhance engraftment of HSCs by modifying the murine osteoblastic niche [83]. HSCs derived from old mice can be rejuvenated when they are put into the young systemic environment [84]. Thus, therapeutic interference counteracting these extrinsic changes may be an alternative or complementary approach to the current strategies focusing exclusively on the HSC themselves.

## CONCLUSION

Despite many exciting discoveries of intrinsic changes in stem cells with aging, there are large gaps in our knowledge regarding the stem cell microenvironmental niche and the effect of age on it [46, 85, 86]. Methods enhancing intimate connections between HSCs and the niche would improve HSC homing and survival, which could further enhance engraftment efficiency [79, 87]. In addition, little is known about stem cell aging in humans, despite a compelling unmet clinical need [88]. Successful clinical HSCT in elderly recipients may require multiple strategies targeting different pathways. With advanced knowledge of induced pluripotent stem cells or embryonic stem cells, we could use these cells as alternative sources of hematopoietic stem/progenitor cells for transplantation in the future.

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## AUTHOR CONTRIBUTIONS

G.V.Z.: final approval of manuscript; Y.L.: manuscript writing, final approval of manuscript.

## DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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