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Rejuvenation of aged hematopoietic stem cells

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ABSTRACT

Until recently, there was broad consensus in the stem cell aging field that the phenotype of aged hematopoietic stem cells (HSCs) is fixed—dominated by cell-intrinsic regulatory mechanisms that cannot be altered by pharmacological or genetic means. The conventional thinking was that HSC aging could not be reverted by therapeutic intervention. This paradigm has started to shift dramatically, primarily because hallmarks of aged HSCs have been successfully reverted by distinct experimental approaches by multiple laboratories. We will discuss in this review these hallmarks of HSCs aging and the novel approaches that successfully ameliorated or even reverted aging-associated hallmarks of aged HSCs.

1. Introduction

Stem cells were initially thought to be endowed with unlimited self-renewal ("rejuvenation") capacity, and thus exempt from aging. This age-associated decline in stem cell function leads to a decline in the regenerative capacity of humans and murine tissues and organs [1–6], which may limit lifespan [2,7,8]. Aging of hematopoietic stem cells (HSCs) is associated with a canonical set of changes in HSCs and their offspring, which will be further introduced and discussed below. These hallmarks of HSCs aging have been reproduced in multiple laboratories. Several reports support that many of these hallmarks/changes are intrinsic to HSCs [9,10]; however but novel data also supports that aging of the bone marrow (BM) niche might be able to confer aging-associated phenotypes on HSCs [11–13].

Recent exciting novel publications indicate that distinct undesirable phenotypes associated with aged HSCs can be ameliorated both pharmacologically and genetically [14–20]. These findings strongly support that the functional decline of aged stem cells may be reversible and that rational interventions can be developed that will target mechanisms of HSC aging to achieve HSC rejuvenation. Identifying conditions under which aged HSCs are activated to become phenotypically and functionally equivalent to young stem cells could be a first step towards designing treatments for age-associated imbalances in hematopoiesis and aging-associated changes in the immune system, thereby allowing for a more healthy aging [21].

2. Hallmarks of aged HSCs

Aging within the hematopoietic system comprises a set of distinct changes, including an increase in the frequency of myeloid cells generated that is linked to an increase in myeloid-related leukemia, as well as a decrease in the output of lymphoid cells (primarily B cells). Also, it includes a reduced regenerative capacity of hematopoiesis upon stress and a decrease in the function of both the innate and adaptive branches of the immune response [9,22,23]. One underlying cellular cause of aging of the hematopoietic system is aging of HSCs. Upon aging the number of phenotypic HSCs increases while their regenerative potential (as determined in serial transplantation assays) decreases [24]. Aged HSCs differentiate preferentially into myeloid cells and show diminished support of the B-cell lineage. Loss of a polar distribution of polarity proteins like Cdc42 and Scribble as well as tubulin in the cytoplasm, and loss of the polar distribution of the acetylated form of the epigenetic marker H4K16 in the nucleus are additional recently identified hallmarks of aged HSCs [18,25]. Aged HSCs also present with changes in their epigenome and altered gene expression profiles [9,18,22,25]. Genome-wide expression studies comparing HSCs from young and old mice indicated that in aged HSCs, expression of genes involved in myeloid development was increased, whereas expression of gene involved in lymphopoiesis

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was decreased. In addition gene sets associated with inflammation, stress response, and senescence were found to be increased in aged HSCs (like clusterin, platelet-selectin, cyclooxygenase 2, Toll-like receptor 4, and the heat shock proteins 5 and 8 [9,10]).

Old HSCs are functionally inferior to their young counterparts with respect to multiple phenotypes. They include a delayed proliferation response in stromal co-cultures, a reduced efficiency for short-term BM homing, and a reduced long-term in vivo self-renewal activity [24].

3. Is Impaired genomic integrity and DNA damage linked to aging of HSCs?

DNA repair maintains genomic stability and loss of DNA repair ability results in genetic instability that may lead to a decline of cellular function. DNA lesions initiate DNA damage response pathways (DDR), which comprise DNA repair but also signal transduction to induce apoptosis or senescence. DNA lesions thus activate a series of signaling pathways including DNA repair, cell cycle checkpoint activation, senescence, and cell death [26–28]. DNA lesions and the DDR also induce chromatin remodeling. While these epigenome and transcriptome modifications brought upon DNA lesions shape the dynamics of the HSCs in the context of self-renewal and differentiation [28–30], the question on whether DNA damage and accumulation of DNA damage with aging contributes to aging of HSCs is still controversially discussed. A number of human genetic abnormalities associated with aging like xeroderma pigmentosa (XP), Cockayine syndrome (CS), trichothiodystrophy (TTD) and those replicated in the mouse like the TTD mouse model and Ercc1$^{-/-}$ mice, suggest that loss of DNA repair pathways may contribute to the aging process [31–33]. Although there is about a two- to threefold increase in mutation frequency in hematopoiesis upon aging [34,35], the increase might still be seen as minor and presents itself with a linear increase in frequency over time. This does not correlate with the exponential increase in for example aging-associated leukemia. Modeling approaches of HSC aging, based on evolutionary theories, further suggest that an accumulation of genetic changes within HSCs is not sufficient to increase HSC fitness, and instead proposes extrinsic microenvironmental mechanisms as the major selective driving force for aging-associated leukemia [36,37]. Additionally, studies conducted in mice deficient for genes involved in several distinct genome maintenance pathways in hematopoiesis (like the nucleotide excision repair genes Xpd and Ercc1 or genes involved in telomere maintenance and non-homologous end-joining like Rad50^{k22m} and Ku80/Ku70) have shown loss of reconstitution capacity, diminished self-renewal, increased apoptosis as well as an early exhaustion of the mutant HSCs [32,38,39]. A general decrease in the number of HSCs does not resemble the observation that physiological aging results in an increase in the number of HSC so the question arises whether aged HSC indeed present with impaired DDR repair pathways. A recent study from our laboratory has demonstrated that the DDR efficiency is not altered upon aging in HSCs in vivo. This is demonstrated by a similar response to DNA damage of both young and old hematopoietic stem and progenitor cells (HSPCs) with respect to cell-cycle checkpoints activation and apoptosis and the accumulation of DNA mutations in response to total body irradiation. Moreover, in a competitive transplantation setting, young and old HSPCs showed identical functional activity in response to irradiation [34]. Thus additional experiments are required to determine whether DDR signaling pathways could represent novel targets for therapies aiming to improve tissue integrity and to prevent cancer development during aging.

4. Novel hallmarks of HSC aging: Altered epigenetic architecture and loss of protein polarity

Regulation of transcription is regulated by epigenetic mechanisms. Epigenetic mechanism are thus also involved in HSCs aging in which several genes for myeloid cell differentiation become upregulated on the expense of lymphopoiesis genes, which are downregulated [10]. These alterations are maintained when old HSCs are transplanted into new recipients [40]. Importantly, epigenetic changes can be inherited to daughter cells, which is an underlying prerequisite for the accumulation of epigenetic changes in HSCs upon aging, similar to DNA mutations. Several components involved in chromatin re-organization and epigenetic maintenance have been reported to become altered upon aging [9]. DNA methylation patterns of old HSCs for instance have been found to be distinct compared to young HSCs, with hypermethylation on regulatory regions associated with HSC differentiation and hypomethylation on genes involved in HSC maintenance [41]. Furthermore, other studies have found that in old HSCs many hypermethylated promoter regions are polycomb group (PcG) target genes and genes regulated by H3K27Me3 and H3K4Me3 histone marks [22,42], which function both to promote and repress gene transcription, respectively. The epigenetic shift and drift can be inherited to daughter cells. In a recent study, Wang et al found that PER2 (period circadian rhythm 2), a transcription factor that binds E-boxes, is upregulated in HSCs upon aging. It also contributes to the induction of DDRs and apoptosis and plays a role in lymphoid lineage potential. Moreover, deletion of Per2 in vivo rescued the diminished lymphoid potential and immune function of old HSCs in a cell-intrinsic manner and led to an elongated lifespan [20]. One explanation for such an observation might be that the transcriptional repression of PER2 on lymphopoietic genes is one of the driving forces for the aging-associated lineage skewing, reinforcing the hypothesis that aged-related changes in HSCs are driven and maintained by an altered epigenetic architecture.

Another study from our laboratory demonstrated that an altered spatial distribution of epigenetic marks in the nucleus contributes to HSC aging. Specifically, the distribution of H4K16Ac (associated with active gene expression) was found to be apolar in nuclei of old HSCs compared to young HSCs, in which it is mostly polar. Polarity is HSCs is controlled by the activity of the small RhoGTPase Cdc42, which is elevated upon aging; treatment with a specific pharmacological inhibitor of Cdc42 activity (CASIN) restored H4K16Ac polar distribution in old HSCs and re-established youthful function of aged HSCs [18].

Are these changes in gene expression levels that are controlled by changes in epigenetics and/or the spatial distribution of epigenetic marks a driving force or rather a consequence of HSC aging? These are unanswered questions. Their resolution will directly contribute to novel approaches to ameliorate HSC aging. Collectively, HSC aging is strongly correlated with changes in epigenetic, transcriptional, and polarity landscape.

Aging in hematopoiesis is also influenced, as more recently discovered, by extrinsic factors like changes of the bone marrow niche upon aging. For example, skewing of aged HSCs towards myeloid differentiation was recently linked to increased secretion of the pro-inflammatory CC-chemokine ligand 5 (CCL5; also known as RANTES) in aged stroma [12]. Furthermore SDF-1, an important chemokine produced by osteoblastic cells in the BM niche which is involved in homing, engraftment, neovascularization, and cell proliferation, was found to be decreased in mesenchymal stem cells (MSCs) of aged mice [11]. This data suggests that altered levels of niche-secreted factors may infer HSC aging-associated phenotypes . Also, differences in the cellular composition of the aged and young BM niche imply that aging of the niche influences the hematopoietic system [13]. Reduction in HSC adhesion to BM stroma cells upon

aging [43] might account for the decrease in HSC self-renewal ability [44]. The increase in adipocytes upon aging negatively regulates hematopoiesis as it delays engraftment [45]. Such extramedullary adipose tissue cells have been recently reported to contribute to the development of aging-associated leukemia by supporting the metabolic demands of leukemic stem cells [46]. So far though, changes in the HSC niche upon aging that account for changes in HSCs upon aging are poorly understood [47,48]. Is the aging-associated epigenetic drift a stem cell-intrinsic mechanism or is it also affected by extrinsic micro-environmental changes in the niche? Whether signals from aged niches directly affect the epigenetic landscape and HSC cell polarity is a novel field of research. A deeper understanding of mechanisms of niche aging might shed new light on distinct mechanisms that contribute extrinsically to aging of HSCs and which might, besides the intrinsic pathways of aging, also become promising targets to ameliorate aging of HSCs.

5. HSC rejuvenation: HSC intrinsic aging mechanisms as a target

Mechanisms of HSC aging involve distinct cell-intrinsic and cell-extrinsic regulatory pathways. The elucidation of mechanisms that affect HSC aging will strongly support approaches to rationally target HSC aging in vitro and vivo. An important milestone in rejuvenation research was the induced pluripotent stem cell (iPSCs) biology introduced by the Yamanaka laboratory. The introduction of four specific genes encoding transcription factors could convert adult somatic cells into pluripotent stem cells [49]. This discovery suggested that by targeting the epigenetic landscape, differentiation can be reverted, which implies that also aging, if primarily driven be epigenetic mechanism, might be reversible. Wahlestedt et al, by reprogramming old HSC into iPSCs and then re-differentiating them into HSCs, demonstrated that the resulting HSCs were functionally similar to young HSCs, thus experimentally demonstrating that HSC aging is reversible by epigenetic reprogramming [40].

In this section, we summarize and interpret recently published data in which intrinsic mechanisms of aging were targeted both genetically or pharmacologically to achieve at least a partial (or segmental) rejuvenation of the function of aged HSCs (Table 1).

5.1. Special AT-rich sequence-binding protein-1 (Satb1)

The chromatin organizer Satb1, an epigenetic regulator of lymphoid progenitor cells, was found to be expressed at a lower level in old HSCs compared to young HSCs. This reduced expression correlated with a decline in HSC function. Overexpression of Satb1 in old HSPCs improved their ability to give rise to lymphoid progeny in vitro [19]. Satb1 might thus be a target to overcome immunosenescence of older adults by enhancing lymphopoiesis.

5.2. Period circadian clock 2 (Per2)

As discussed above, Per2 is upregulated upon aging in lymphoid-biased HSCs and stimulates the DDR and p53-dependent apoptosis. The deletion of Per2 in old HSCs attenuated the aging-associated myeloid/lymphoid skewing of hematopoiesis upon physiological aging, as well as telomere shortening in lymphoid cells in vivo. This resulted in an increased immune function and elongated lifespan of prematurely aging mice [20]. Per2 might thus be another novel therapeutic target to restore lymphoid potential in an aged HSC compartment.

5.3. Sirtuin 3 (Sirt3)

Sirt3, a mammalian sirtuin that regulates mitochondrial de-acetylation, becomes downregulated in HSPCs upon aging, which correlates with an increase in reactive oxygen species (ROS) production and an increase in oxidative stress in HSPCs. Interestingly, overexpression of Sirt3 in old HSCs decreased ROS production and increased the reconstitution potential of most blood cell lineages [14], while the relative contribution of myeloid cells remained though at the level of aged HSCs.

5.4. Sirtuin 7 (Sirt7)

Sirt7, a mammalian sirtuin that regulates promoter de-acetylation, interacts with nuclear respiratory factor 1 (NRF1), a master regulator of mitochondria. SIRT7 represses NRF1 activity to suppress mitochondrial activity and proliferation. Aged HSCs present with a reduced expression of SIRT7. Genetic SIRT7 inactivation caused reduced HSCs quiescence and an increased mitochondrial protein folding stress [PFS(mt)] response and a compromised regenerative capacity of hematopoietic stem cells (HSCs). SIRT7 overexpression or NRF1 inactivation in aged HSCs reduced PFSmt, improved the HSCs reconstitution capacity and rescued the myeloid-biased differentiation of aged HSCs. These findings defined the deregulation of the mitochondrial stress-mediated metabolic checkpoint as a reversible factor contributing to HSC aging [50].

5.5. Mammalian target of rapamycin (mTOR)

mTOR is an important nutrient-sensing protein that has been implicated in organism longevity [51]. mTOR shows an elevated activity in aged HSCs, which was linked to a relative decrease in lymphopoiesis and an impaired capacity to reconstitute the hematopoietic system [16]. Treatment of aged mice with the mTOR inhibitor rapamycin increased their lifespan, reduced the number HSCs to a youthful level, restored youthful HSC self-renewal properties, and resulted in an improved vaccination response against a lethal challenge with influenza virus [16]. Because inhibition of mTOR signaling via rapamycin has been involved in regulating longevity of organisms [52], targeting the mTOR pathway might not only result in the rejuvenation of the hematopoietic system but might also contribute to attenuate aging of whole organisms.

5.6. Prolonged fasting

Prolonged fasting of aged mice of up to 72 hours has been found to reduce the frequency of myeloid-biased HSCs, promote a youthful HSC self-renewal ability and regenerative capacity upon serial transplantation. Mechanistically, prolonged fasting resulted in reduced circulating insulin-like growth factor-1 (IGF-1) levels and reduced protein kinase A (PKA) activity that correlated with a restoration of youthful levels of HSC intrinsic nutrient sensing [17]. Investigations of whether prolonged fasting can improve aging-associated immunosenescence in humans are then of high interest, not only for vaccination approaches but also in the context of tissue regeneration modified by immune cells as well as novel cancer immune-therapy approaches.

5.7. Inhibition of Cdc42 activity (by CASIN)

Ex vivo treatment of aged HSCs with CASIN, a specific pharmacological inhibitor of Cdc42 activity, functionally rejuvenated old HSCs with respect to several phenotypes associated with HSC aging [18]. Elevated activity in aged HSCs is driven by a shift from

Table 1
Interventions that contribute to HSCs rejuvenation.

Target proteins	Type of intervention	Rejuvenation phentotype(s)	References
Satb1	Genetic	Overexpression enhances lymphoid progeny	[19]
Per2	Genetic	Deletion attenuates lymphoid/myeloid skewing	[20]
Sirt3	Genetic	Overexpression decreases ROS production Increases the reconstitution potential	[14]
Sirt7	Genetic	Overexpression reduces PFSmt Improves reconstitution capacity Rescues myeloid-biased differentiation	[50]
mTOR	Pharmacologic	Inhibition increases life span Reduces the number HSC to a youthful level Restores youthful HSC self-renewal upon transplantation	[16,52]
Prolonged fasting	Pharmacologic	Reduces the frequency of myeloid-biased HSCs Restores youthful HSC self-renewal ability and regenerative capacity upon serial transplantation	[17]
Cdc42	Pharmacologic	Inhibition enhances competitive repopulation Reduces the frequency of myeloid-biased HSCs	[18]
BCL-2	Pharmacologic	Inhibition depletes senescent HSCs in the BM Attenuates lymphoid/myeloid skewing	[15]
BCL-xL		Improves reconstitution potential of HSCs upon serial transplantation	

canonical to non-canonical Wnt signaling due to an increase of Wnt5a expression in old HSCs [53]. Experiments are underway to test inhibition of Cdc42 activity in vivo. Elevated Cdc42 activity upon aging is not restricted to the hematopoietic system. Inhibition of Cdc42 activity in vivo might thus also target non-hematopoietic tissues.

5.8. ABT263

Chang et al recently demonstrated that ABT263, a specific inhibitor of the anti-apoptotic proteins BCL-2 and BCL-xL, induced apoptosis of senescent cells. Oral administration of this potent novel senolytic drug to either sublethally irradiated or aged mice effectively depleted senescent HSCs in the bone marrow. This resulted (in the case of old animals) in a rejuvenation of the pool of old HSCs, which after treatment with ABT263 showed less myeloid biased and improved reconstitution potential upon serial transplantations [15]. Because ABT263 treatment also abrogated the senescence-associated secretory phenotype (SASP) response in BM stromal cells, it would be of particular interest to investigate whether the rejuvenation effect of ABT263 on old HSCs in vivo might be also due to depletion of senescent cells in the BM microenvironment.

6. Targeting aging of the HSC niche for HSC rejuvenation

Age-related changes in the local BM niche microenvironment influence the aging-associated decline in HSCs function. BM niche signals such as locally secreted cytokines have been already described in regulating HSC fate [54]. Age-related changes in stroma secreted factors like CXCL12 (down upon aging) and Rantes/Ccl5 (up upon aging) have been identified to regulate HSC function and myeloid differentiation upon aging [12]. Furthermore, an increase of oxidative stress, inflammation and a decrease of the extent of hypoxia have been associated with aging of the niche [55]. In general, the degree by which an aged niche influences HSC aging remains to be further investigated.

Given a role for the aged niche in conferring aging on HSCs, establishing strategies to target and rejuvenated the aged niche might be a novel tool to rejuvenate HSCs. For example, in a recent study Kathri et al reported that there is an accumulation of ROS in aged $CD45^{-}$ BM stromal cells, which leads to their death via apoptosis [56]. Treatment of old stroma cells with curcumin, a natural antioxidant agent, reduced these high ROS levels and subsequently the high levels of apoptosis, and reduced the expression of the stress-responsive genes *Nox-1*, *Sod-2,* and *Gpx-1*. Moreover, treatment of 18-month-old animals with curcumin improved BM cellularity and thus hematopoietic reconstitution upon transplantation of BM cells compared to transplants into old nontreated animals. Another more recent study demonstrated that sex steroid ablation (SSA) induced hematopoietic and lymphoid recovery by enhancing self-renewal of old HSC, as well as lymphoid differentiation through both HSCs intrinsic mechanisms but also via upregulation of factors like Opn, Ang1, Cxcl12, Scf, Tgfb, Jag1, and Vcam1 in endothelial cells, pre-osteoblasts, and mature osteoblasts of old mice. Many of these factors are directly regulated by a known "aging gene", FOXO1 [57]. Collectively, these data imply that modulation of factors in the niche can offer novel targeted strategies for HSC rejuvenation.

7. Conclusions/outlook

Recent developments have identified molecular mechanisms of aging of HSCs, driven both by cell intrinsic mechanisms and by aging of the stem cell niche. Based on these findings, novel genetic or pharmacological approaches were developed. They demonstrate that unwanted aging-associated changes of HSCs function can be ameliorated or sometimes even reverted to a youthful level and thus rejuvenated. These are promising findings towards designing treatments for aging-associated imbalances in hematopoiesis and aging-associated changes in the immune system to achieve healthy aging. There is evidence that an aged hematopoietic and immune system might also affect aging-associated changes in solid organs. For example, aging-associated reduced clonality in the human hematopoietic system strongly correlated to a higher incidence of cardiovascular disease [58]. Novel experiments are thus warranted to test in as much a rejuvenated hematopoietic system might also be able to contribute to amelioration of unwanted aging-associated changes in other organ systems.

Conflicts of interest

The authors declare no conflicting financial interests.

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