CellPress
OPEN ACCESS

Cell Stem Cell Hallmarks

Review

Hallmarks of stem cell aging

Thomas A. Rando,[1,2,*] Anne Brunet,[3,4,*] and Margaret A. Goodell[5,6,*]
[1]Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Biology, University of California, Los Angeles, Los Angeles, CA, USA
[2]Department of Neurology, University of California, Los Angeles, Los Angeles, CA, USA
[3]Department of Genetics, Stanford University, Stanford, CA, USA
[4]Glenn Center for the Biology of Aging, Stanford University, Stanford, CA, USA
[5]Molecular and Cellular Biology Department, Baylor College of Medicine, Houston, TX, USA
[6]Stem Cells and Regenerative Medicine Center, Baylor College of Medicine, Houston, TX, USA
*Correspondence: trando@mednet.ucla.edu (T.A.R.), anne.brunet@stanford.edu (A.B.), goodell@bcm.edu (M.A.G.)
https://doi.org/10.1016/j.stem.2025.06.004

SUMMARY

As organisms age, somatic stem cells progressively lose their ability to sustain tissue homeostasis and support regeneration. Although stem cells are relatively shielded from some cellular aging mechanisms compared with their differentiated progeny, they remain vulnerable to both intrinsic and extrinsic stressors. In this review, we delineate five cardinal features that characterize aged stem cells and examine how these alterations underlie functional decline across well-studied stem cell compartments. These hallmarks not only provide insight into the aging process but also serve as promising targets for therapeutic strategies aimed at rejuvenating stem cell function and extending tissue health span.

INTRODUCTION

Somatic stem cells, often referred to as adult stem cells, engage in the maintenance of tissues through homeostatic turnover and in the repair of tissues through regenerative responses. As such, these stem cell populations must have evolved mechanisms to sustain themselves over the scaled lifespans of organisms whose tissues they maintain,[1] and yet, as organisms of different lifespans age, the decline of these stem cell functions is apparent in terms of impaired tissue homeostasis and regeneration in response to injury or disease.[2–5]

In this review, we describe key functional hallmarks of stem cells that change with age (Figure 1). We have focused on functional aspects as opposed to molecular characteristics or proposed drivers for several reasons. First, the key drivers of cellular aging, such as genomic instability, altered proteostasis, mitochondrial dysfunction, and epigenetic changes,[6] affect all cells. As such, stem cell aging is not unique in terms of molecular and functional drivers. Second, the molecular features of aged stem cells differ from tissue to tissue, with some themes emerging but tremendous variability among stem cell populations. Most importantly, we wanted to focus on functional hallmarks that are either unique to stem cell physiology or at least are key defining features related to the role that stem cells play in tissue homeostasis and repair. These functional hallmarks manifest at the single-cell level, at the population level, or both. Notably, the hallmarks of stem cell aging are at the intersection of the hallmarks of stem cells and those of aging,[6,7] highlighting features at that interface.

Although there are many types of stem cells throughout the body, and even multiple subtypes within individual tissues and organs, we will focus on the populations that have received the most scrutiny in terms of their age-related functional changes. Those populations include hematopoietic stem cells (HSCs), neural stem cells (NSCs), muscle stem cells (MuSCs), intestinal stem cells (ISCs), and a variety of stem cells in the skin, including epidermal stem cells (EpSCs), melanocyte stem cells (McSCs), and hair follicle stem cells (HFSCs). We will also focus primarily on stem cell aging in mammalian systems since they account for most of the studies in this area.

Before we expand upon each hallmark individually, there are several considerations worth raising that relate to many stem cell populations. First, we note that somatic stem cells are responsible for both homeostatic maintenance and regeneration of a wide variety of tissues. However, these two functions may be quite distinct. Stem cell proliferation associated with tissue homeostasis is generally continuous and occurs in absence of any trigger from cellular injury. By contrast, tissue repair and regeneration in response to damage (e.g., in the setting of trauma, ischemia, and other injuries) typically elicit an acute, transient, and potentially massive regenerative response. In those settings, stem cell-mediated repair occurs in a more complex microenvironment that includes inflammation and cellular debris associated with tissue necrosis. Thus, age-related changes in stem cell functions may differentially impact the homeostatic versus regenerative/repair aspects of stem cell activity.

Aspects of the hallmarks of aging stem cells may be cell intrinsic, may arise from cell-extrinsic influences, or a combination of the two. Intrinsic changes would reflect molecular alterations acquired by the stem cell as a result of the passage of time. These would include somatic mutations that are essentially irreversible and might affect stem cell function. Epigenetic changes that perdure over time would also be an example of an intrinsic change. Extrinsic influences would relate to the changes in the stem cell niches and the systemic environment. For example, aging is accompanied by a general increase in inflammation. This aged inflammatory environment affects the

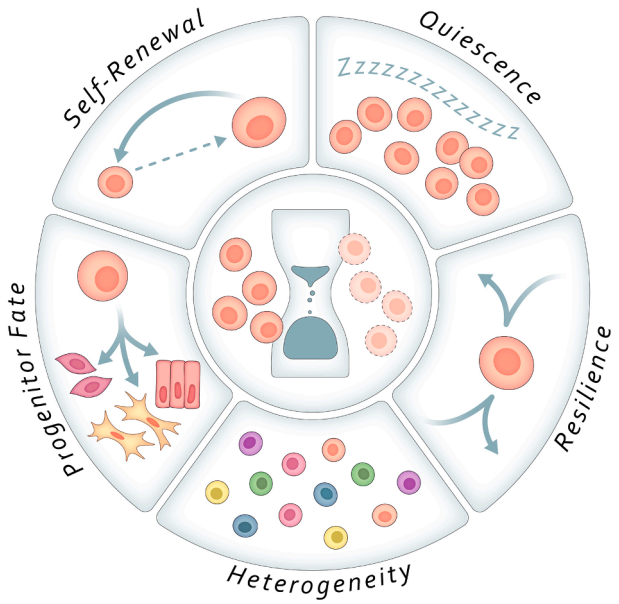

Figure 1. Hallmarks of stem cell aging
We review five hallmarks whose changes are fundamental to the functional decline of aged stem cells in terms of their ability to maintain tissue homeostasis or engage in tissue regeneration.

output or behavior of stem cells. Likewise, the accumulation of senescent cells in the stem cell niche may negatively impact stem cell function via paracrine factors. In principle, these effects could be largely reversible if the environment were modified, for example by reducing inflammation or eliminating senescent cells.

With these premises, considerations, and caveats, we turn to the descriptions of the hallmarks of stem cell aging. For each hallmark, we provide representative examples of how they change with age in one or more stem cell compartments rather than provide an exhaustive list for all stem cell compartments. The hallmarks that we have selected to highlight reflect fundamental characteristics of stem cell function (Figure 1): (1) depth of quiescence, (2) self-renewal propensity, (3) fate of progeny, (4) resilience, and (5) population heterogeneity. These functions play key roles in the typical stem cell lineage progression from quiescence to differentiation (Figure 2).

HALLMARKS OF STEM CELL AGING

As we embark on a description of the hallmarks of stem cell aging, one recurring theme is that aging may result in either an increase (in a kind of "gain-of-function" mode) or a decrease (in a kind of "loss-of-function" mode), each of which results in an impairment of stem cell functionality. These examples only highlight the balance of inputs that are required for effective stem-cell-mediated tissue homeostasis and repair. Another recurrent theme is the extent to which any single hallmark highlighted is characteristic of individual stem cells (e.g., depth of quiescence) or is instead a characteristic of the population (e.g., heterogeneity). The latter emphasizes the complex interactions between heterogeneous populations of stem cells as well as between stem cells and their environment to produce complex differentiated tissues.

One obvious change that occurs in many stem cell populations with age affects the number of stem cells in the tissue as quantified by in situ analyses, such as by immunostaining, or by *ex vivo* analyses, such as by flow cytometry or single-cell-based "omics" approaches. As cell number is not a functional readout, we have not listed changes in numbers as a key hallmark of stem cell aging. Rather, we have focused on functions, such as self-renewal or mechanisms of resilience, whose change with age can result in either a loss of stem cells or an increase in the stem cell pool size.

Changes in depth of quiescence

Most somatic stem cell populations (e.g., HSCs, NSCs, MuSCs, and HFSCs) persist in a quiescent state. They rarely divide, only then giving rise to proliferating progenitors (often called "transit amplifying" [TA] cells) that sustain tissues during homeostasis and have the capacity for extensive proliferation during regeneration. Quiescence is a state of cell cycle withdrawal, which, unlike terminal differentiation or senescence, is readily reversible.[8] Thus, quiescent stem cells can exit the quiescent state and enter the cell cycle, while some fraction of their progeny return to quiescence via self-renewal. The quiescence state, with its lower and unique metabolic activity (e.g., dependency on fatty acid oxidation [FAO]),[9–11] allows for the persistence of stem cell populations in tissues over the lifespan of an organism, a feature that is particularly important in long-lived organisms, such as humans.

There are notable exceptions to the generalization of stem cell populations persisting in a quiescent state. Both ISCs and EpSCs persist in a state of continuous proliferation and appear to be able to generate progeny with negligible decline during aging.[12–14] The mechanisms by which these cells are able to sustain seemingly unlimited proliferative potential without undergoing replicative senescence or substantial decline in proliferative output remains a mystery.

For many quiescent stem cell populations, alterations in the depth of the quiescent state with age have been reported. These states include deeper quiescence in which the kinetics of activation are slower and more shallow quiescence in which the kinetics of activation are accelerated (Figure 3). In muscle, there is an emergence of a subset of MuSCs that exhibit a deeper quiescent state with age,[15] and this state is associated with impaired muscle regeneration. This subset was found to have lower levels of glutathione, and the restoration of glutathione levels could rescue this aging phenotype.[15] However, there is also evidence of a population of aged MuSCs that exhibit a shallower state of quiescence, entering the cell cycle readily and failing to self-renew, thus contributing to the decline in MuSC numbers with age.[16] The loss of quiescence maintenance among this MuSC subpopulation is due to an increase in FGF2 secreted into the MuSC niche from muscle fibers.[16] Inducing a shallow state of quiescence, termed G_{Alert},[17] by enhancing mTOR signaling leads to depletion not only of MuSCs, but also of ISCs and stem cells in the trachea.[18] Bulk RNA sequencing (RNA-seq) analysis of MuSCs exhibiting these different states of quiescence have revealed distinct transcriptomic signatures.[15,17] Single-cell RNA-seq analysis of MuSCs in different

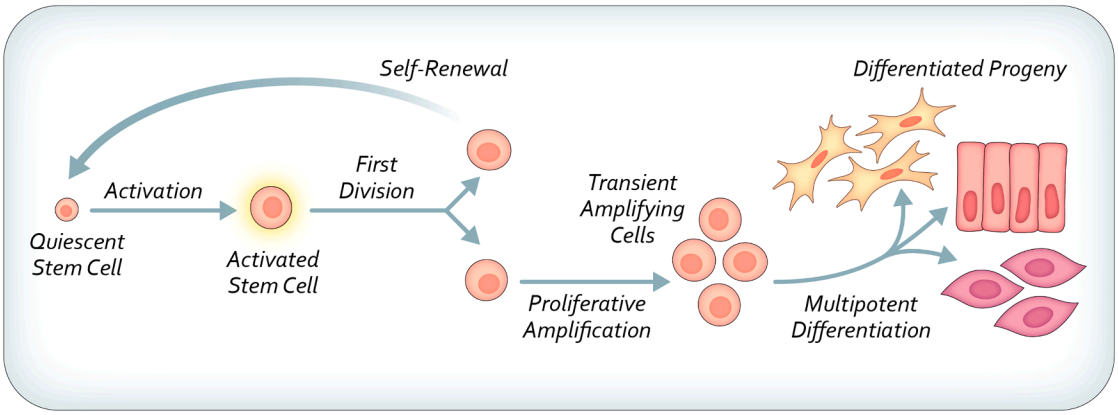

Figure 2. Youthful stem cell functionality

Normal functions of stem cells are illustrated, including hallmarks that change with age. "Resilience" is reflected by the absence of cell death during these processes in young organisms. Heterogeneity is a property of the whole stem cell population and is thus not included in this illustration of the functions starting with a single stem cell.

experimental states, which have been done extensively,[19,20] are likely to reveal subsets of cells in different depths of quiescence by their transcriptomic profiles. A continuum of intermediate states probably exists between quiescence and activation, adding complexity to the changes in the depth of quiescence to stem cell aging.[21,22]

In the brain, quiescent NSCs are found primarily in two specific regions—the dentate gyrus of the hippocampus and the subventricular zone (SVZ) along the walls of the lateral ventricles. There is evidence that deeper NSC quiescence is one process that prevents NSC activation and leads to reduced neurogenesis with age in the SVZ and hippocampus.[23–25] This increase in quiescence depth is in part a result of signals from the NSC niche, including the Wnt antagonist sFRP5. Blocking those niche signals restores aged neurogenesis back toward youthful levels. The suppression of NSC activation out of the quiescent state may also be a result of inflammatory signals originating from T cell infiltration into the aged NSC niche or changes in metabolism.[26,27] Interestingly, sub-populations appear to be in shallower quiescence ("resting") and deeper quiescence ("dormant"), with the former contributing more actively to neurogenesis in the young brain but the latter accounting for persisting, albeit lower, levels of neurogenesis at older ages.[25,28,29] Cells in deeper quiescence exhibit gene expression changes in several pathways associated with aging, including changes in inflammation, metabolism, proteostasis, and DNA repair.[25] In the hippocampus, deepening quiescence of the dormant NSCs with age correlates with the decreased expression of ASCL1, a gene required for the activation of a pool of NSCs.[30] Moreover, chronic *in vivo* imaging shows that aging reduces the clonal output of each individual NSCs, by increasing quiescence.[31] In the SVZ, lineage tracing also revealed increased quiescence of a pool of NSCs.[24]

For HSCs, the niche is the bone marrow stroma, with several specialized cell types that support stem or progenitor cells, particularly endothelial cells and perivascular leptin-receptor-positive cells.[32] These niche cells produce stem cell factor and the chemokine CXCL12, which are important for the maintenance of HSCs.[33,34] Among the many changes that occur in the HSC population with age is a reduced growth factor responsiveness.[35] This altered responsiveness manifests not only as a reduced proliferative response, but also as a delay in reactivation after the exit of quiescence and subsequent first division, consistent with the idea of a deeper quiescent state. These changes were found to be correlated with a preferential reduction in Akt signaling in aged HSCs.[35] More broadly, changes in the cellular composition of the niche with age may affect the function and activity of HSCs. For example, increases in adipocytes in the aging bone marrow can increase inflammation, which is known to negatively affect HSCs. Similarly, age-related changes that affect the proportion of megakaryocytes could influence HSCs through secretion of different factors.

Changes of self-renewal propensity

Changes in the propensity of stem cells to undergo self-renewal (Figure 4) reflect a special example of an alteration of the fate of stem cell progeny. Typically, the self-renewal process is a result of the asymmetric division of a stem or progenitor cell.[36,37] Self-renewal ensures the preservation of the stem cell pool rather than generation of specialized tissue. Therefore, abnormalities of self-renewal may account for increases or decreases in stem cell numbers as organisms age.

With age, HSCs exhibit an increased propensity to self-renew at the expense of differentiation,[38,39] resulting in a gradual increase in the size of the long-term HSC pool. At the same time, there is a gradual decrease in the functional regeneration capacity of stem cells on a per stem cell basis, measured by competitive bone marrow transplantation assays.[40] The net effect is an overall maintenance of stem cell activity across the pool. Importantly, some of the functional activity lost with age can be regained when stem cells are placed in a young environment by transplantation; however, much of the decline in activity appears difficult to be reversed by the milieu alone.[41] This apparent increase in stem cell numbers may be driven by somatic mutations (e.g., in *Dnmt3a* or *Tet2* that increase self-renewal and impair differentiation).[42] Likewise, environmental changes can promote the expansion of some stem cell subtypes over others. The overall outcome may appear similar in terms of increased stem cell

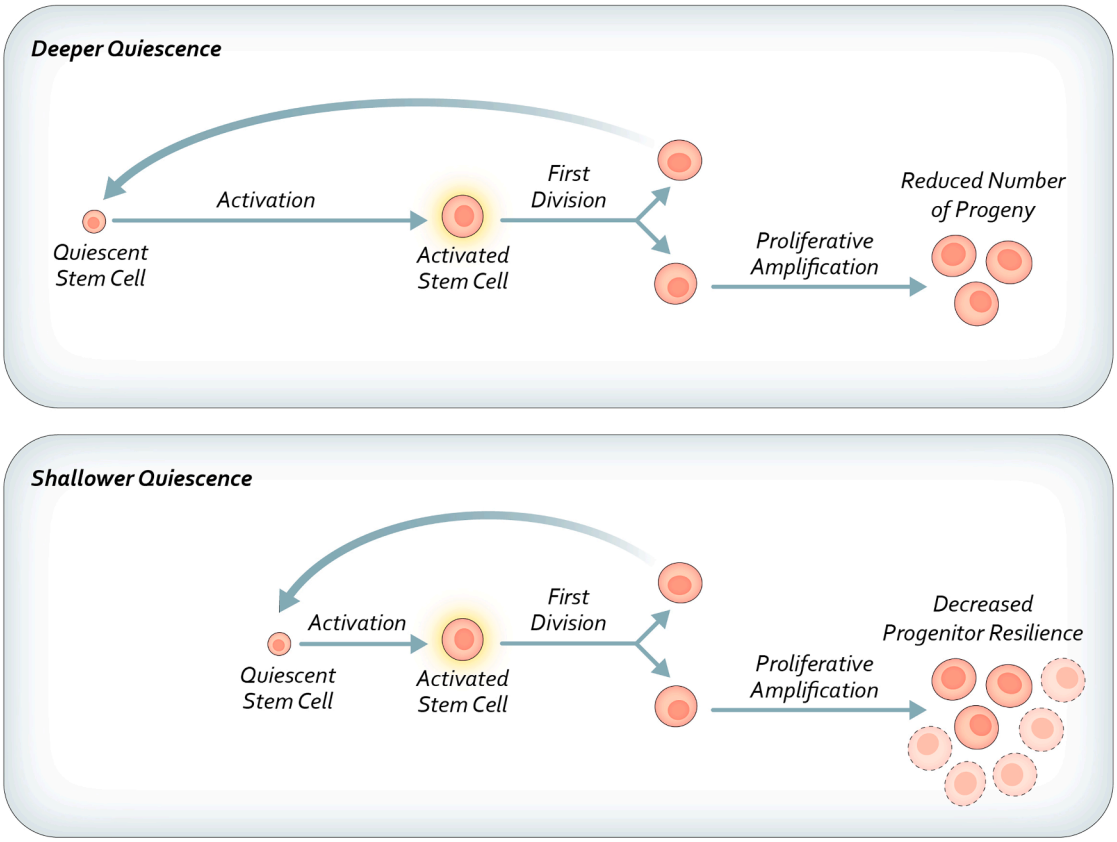

Figure 3. Alterations in stem cell quiescence with age

Increases and decreases in the depth of quiescence, resulting in longer and shorter times required for activation, respectively, have been reported in aged stem cells. Stem cell activation from deep quiescent states has been associated with reduced production of differentiated progeny. Stem cell activation from shallow quiescence has been associated with an overproduction of TA cells and reduced survival.

numbers, but the mechanisms (several of which are possible with aging) may have different implications. For example, stem cell expansion due to mutations that cause clonal hematopoiesis (CH) is accompanied by a higher risk of malignancy development and other aging-associated diseases.[43]

Adult neurogenesis is maintained by symmetric self-renewal and differentiation.[44] With age, NSCs exhibit an increased propensity for asymmetric division in the SVZ.[24] Aging is also accompanied by a decrease in neural progenitor proliferation.[45] NSC self-renewal potential declines with age, and contributes to the reduction of NSCs in the aged brain.[46] This is due, among many other changes, to a gradual decline in the expression of the transcriptional regulator Hmga2 which, in young mice, promotes NSC self-renewal by reducing the expression of the tumor suppressors, $p16^{Ink4a}$ and $p19^{Arf}$.[46] Indeed, age-dependent increase in $p16^{Ink4a}$ expression reduces NSC progenitor proliferation.[47]

It should be noted that different tissues use different mechanisms to maintain or renew their quiescent stem cell populations, and the impact of aging on these processes has not been well studied. For example, in the intestine in addition to the continuously proliferating ISCs, there is another population of stem cells, the so-called "+4 cells,"[48] that are quiescent and serve as a reserve population under conditions of increased regenerative demand. To date, no comparable quiescent population has been identified in the epidermis. Nevertheless, this model of a tissue having a population of rapidly proliferating progenitors, which themselves possess potential for both self-renewal and differentiation, as well as a population of dormant reserve cells, may be a common mechanism. The intestine also seems to have a parallel mechanism to replenish differentiated cells. Tuft cells are differentiated cells in the epithelium capable of giving rise to stem-like cells.[49] There are other examples of more differentiated epithelial cells that can revert back to a more stem-like state,[50] suggesting that various tissues may have evolved mechanisms for replacing quiescent stem cells or maintaining tissue repair even without replenishing the stem cell pool. A report about the dynamics of McSCs in the skin suggests dormant stem cells self-renew by first giving rise to a proliferative population of TA cells, which, while generating more differentiated melanocyte progeny, also give rise to rare cells that will return to dormancy and migrate to the stem cell niche.[51] How these various processes are altered during organismal aging has not been studied in detail.

Altered cell fate

One of the most-studied features of aging stem cell populations is the impairment of tissue homeostasis or repair because of

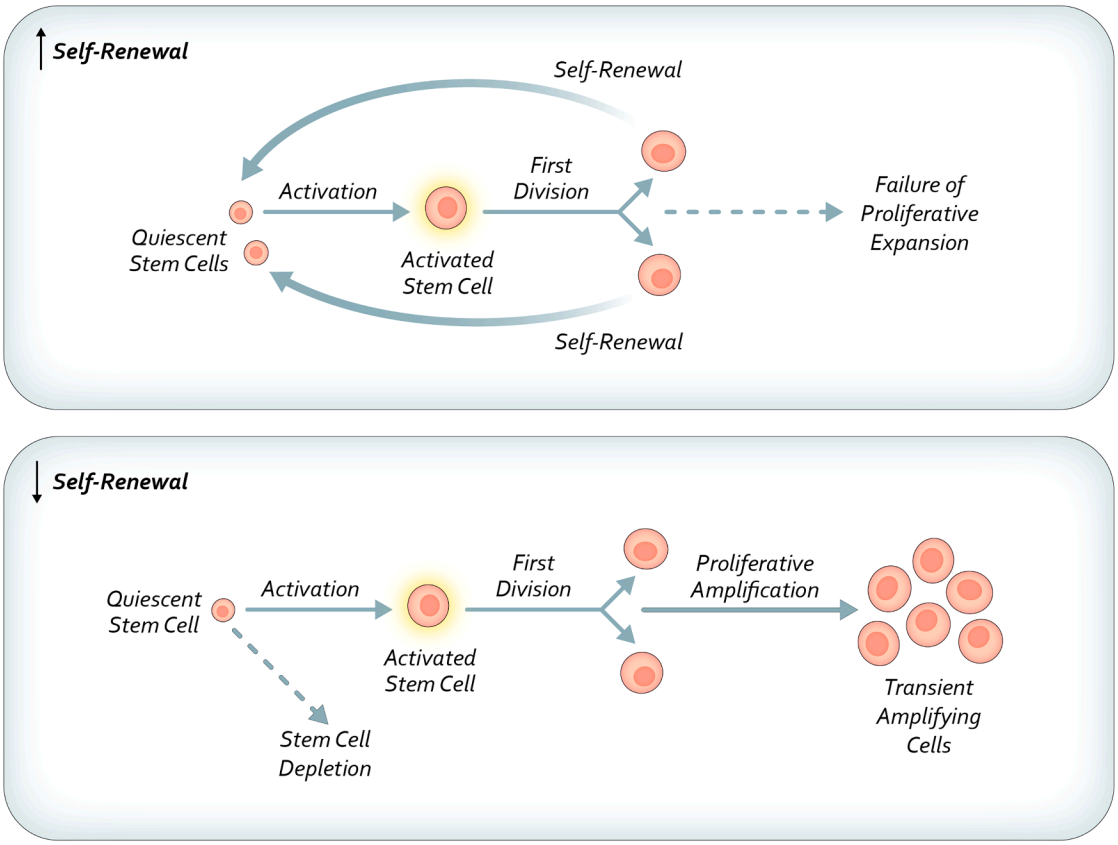

Figure 4. Alterations in stem cell self-renewal with age

Increases and decreases of self-renewal propensity have been described for aged stem cells. An increased self-renewal propensity comes at the cost of reduced output of differentiated progeny. By contrast, a decreased propensity to self-renew leads to the gradual depletion of the stem cell pool.

altered differentiation trajectories of stem cell progeny. These age-related changes can manifest as skewed differentiation or aberrant gain of an alternative differentiation potential. In either case, the resulting progeny represent populations that differ in old tissues compared with young. A change in self-renewal potential was already discussed previously. In some cases, we have highlighted cell-extrinsic changes in the stem cell niche or systemic environment that contribute to the changes in progeny cell fate in aged animals. However, it is likely that all cases of altered fates of stem cell progeny are due to a combination of cell-intrinsic changes and external factors.

Skewing of differentiation fates

In multipotent stem cells, progeny typically differentiate along a normal distribution, but this distribution can change with age (Figure 5A). One common age-associated change in the population of stem cell progeny occurs in the hematopoietic system, although this is not strictly a change in cell fate of individual cells. HSCs are now known to represent a pool of cells with slightly different propensities. With age, myeloid cell production increases, whereas lymphoid production decreases, thus contributing to a variety of hematologic disorders.[38,52–55]

In the adult hippocampus, where NSCs give rise to neurons and other cells, such as astrocytes, the differentiation potential becomes skewed with age. Through a series of asymmetric cell divisions, neural progenitors exhibit a decline in the generation of new neurons and a conversion into astrocytes, which represent a terminal state of differentiation.[56] Thus, the age-related decline in neurogenesis is accompanied by an increase in the formation of new astrocytes.[57] In aged ISCs, there is a skewing of differentiation toward more secretory cells (goblet and Paneth cells).[58] This altered differentiation trajectory is associated with a loss of Wnt signaling in ISCs, and restoration of Wnt signaling can rescue this aging phenotype in the intestine.[58]

Abnormal cell fates

In addition to the skewing of normal fates of multipotent adult stem cells, aging may also be associated with aberrant cell fates as stem cells exit quiescence and proliferate (Figure 5B). Below, we highlight two specific categories—when stem cells adopt aberrant lineages and when they undergo malignant transformation. We end this section with a discussion of how senescence in the stem cell niche or even in distant tissues may negatively impact stem cell function.

Aberrant lineages. In muscle, aging leads to an increased propensity of MuSCs to adopt a fibrogenic lineage, losing their myogenic potential and contributing to age-related fibrosis.[59] The increased stiffness of aged extracellular matrix drives MuSC fibrogenic conversion.[60] This propensity is reversible as heterochronic parabiosis can restore the myogenic potential of an aged MuSC population back toward levels seen in young animals.[59] MuSCs also have a tendency to activate an adipogenic

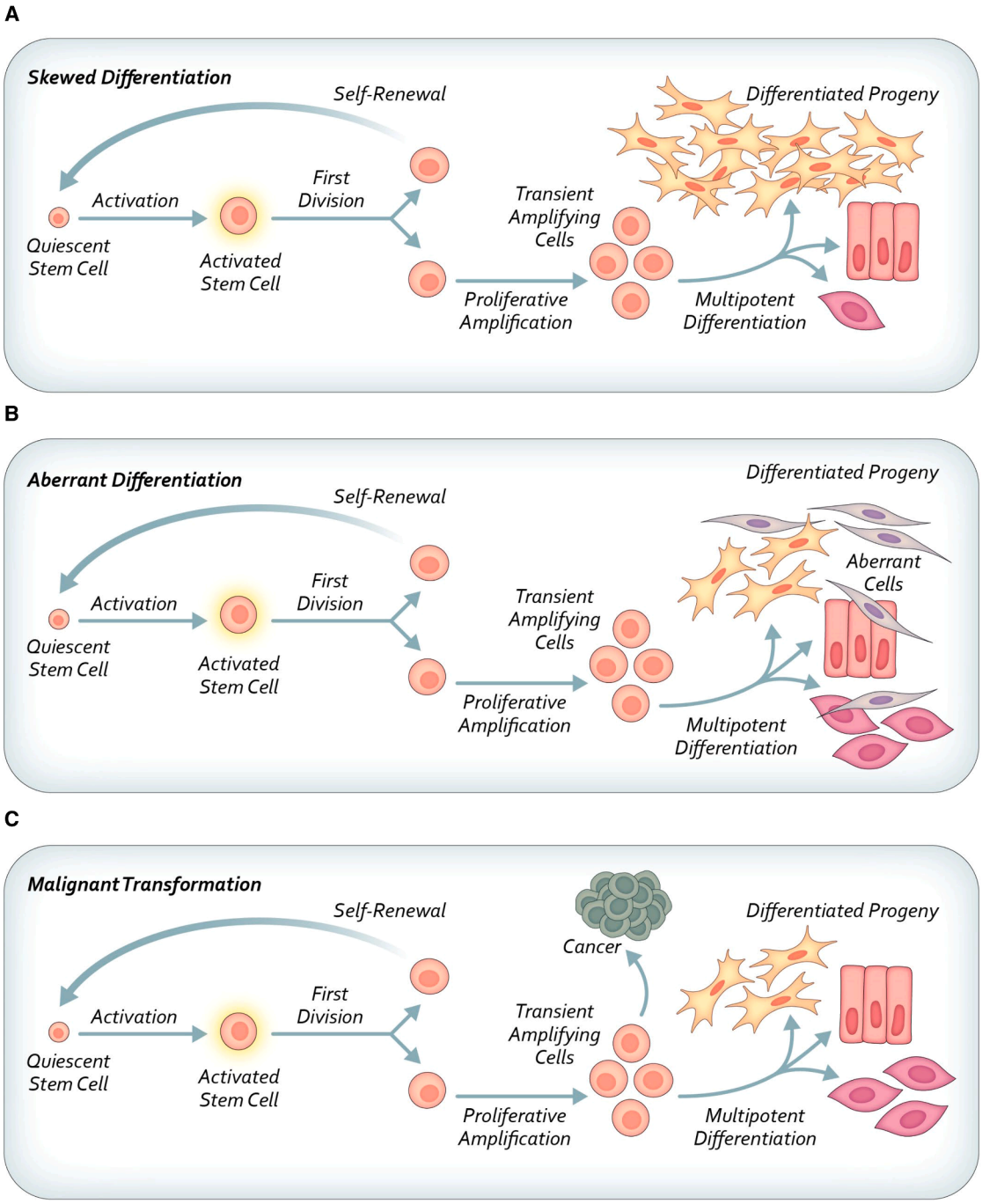

Figure 5. Age-related changes in the fates of stem cell progeny

With age, alterations in stem cell differentiation can impact the health of the tissues to which the stem cells give rise.
(A) "Skewed differentiation" illustrates a shift in the balance of normally differentiated progeny in favor of one lineage and at the expense of others.
(B) "Aberrant differentiation" shows the production of novel, non-functional differentiated progeny at the expense of normal cells.
(C) "Malignant differentiation" refers to the potential for stem cells and progenitors to undergo malignant transformation as cells of origin for cancers.

programs with age,[61] although this does not seem to contribute to intramuscular fat accumulation as seen in aged muscle.

In the bone marrow niche for HSCs, mesenchymal stromal cells (MSCs) support hematopoiesis.[62] With age, these MSCs increasingly give rise to adipocytes,[63] contributing to the increased fatty marrow that is observed in aged individuals. In addition, aged MSCs also progressively produce cells that adopt senescent phenotypes.[64] These aberrant fates are associated with widespread changes in the MSC epigenome.[65]

In aging mice and the non-human primate, the gray mouse lemur, the decrease in neurogenesis from NSCs in the SVZ is accompanied by an increase in the generation of

oligodendrocyte precursors, a fate that is rarely observed in young animals.[66] In both species, this change in cell fate propensity is accompanied by an increase in myelin content in the corpus callosum. Aged HSCs also produce higher numbers of aberrant megakaryocytes that arise in parallel to the normal production of platelets.[54] These abnormal platelets can lead to increased thrombosis in vivo.

Malignant transformation. Cancer is largely a disease of aging. How stem cells contribute to cancer with age is an ongoing area of interest. Broadly, cancer requires the acquisition of genetic and/or epigenetic changes within a long-lived cell that eventually leads to transformation. Stem and progenitor cells are generally the longest-lived cells that still retain the capacity to divide. For this reason, they are thought to be a reservoir for the emergence of cancer (Figure 5C). Consistent with the notion of the stem cell being a key component is the correlation between common malignancies and tissues with high stem cell turnover.[67]

Importantly, many mutations in genes that drive clonal expansion (and loss of heterogeneity, discussed below) also contribute to the development of malignancies over time. For example, mutations in *DNMT3A* are the most frequent driver of CH, and these mutations are also considered to be a major driver of several hematologic malignancies.[68] Mutations in *DNMT3A* can arise in HSCs decades earlier than development of malignancies. The mutation is thought to drive an expansion of the HSC pool,[69,70] providing a larger target population for secondary hits to act on, as well as altering the cells epigenetically and metabolically to enhance the likelihood of transformation. Still, secondary and tertiary mutations, such as in *NPM1* and *FLT3*, are required for the development of acute myeloid leukemia.[71]

Similarly, mutations in *TP53*, found in non-malignant progenitor expansions in many tissues, often contribute to cancer development. Cells bearing the TP53 mutation are found circulating in blood cell progeny years before the malignancies develop.[72] Environmental exposures favor the survival and expansion of TP53-mutant clones over WT clones, ultimately leading to fulminant growth with cells carrying numerous additional genetic lesions thought to contribute to transformation. Similarly, stem cells bearing *TET2* or *DNMT3A* mutations are more resilient to inflammation, such that in an inflammatory environment (found in aging or other pathologic states), those variant cells are more able to expand and outcompete WT counterparts.[73]

While less well studied outside the hematopoietic system, these principles likely hold in other tissues. For example, normal human endometrial tissue consists of multiple glands generated via stem cells. The stem cells slowly accumulate mutations (~29/year), which then contribute to the glands.[74] Many of the genes which accumulate mutations are thought to have the potential to contribute to malignancy development. However, despite accruing on the order of 1,500 mutations by the fifth decade of life, with many glands having known cancer-driver mutations in genes such as *KRAS* or *PIK3CA*, endometrial cancer is relatively rare, and the malignancies have around five times the number of mutations. Additional processes are likely necessary to drive malignancy, the seeds of which originate in the stem cells that regenerate the endometrial glands. Similarly, in mouse models, malignant astrocytomas can originate from neuronal stem cells,[75] and different CNS progenitors may lead to distinct glioblastoma subtypes.[76]

Importantly, the aging environment clearly promotes malignancies, but the mechanisms are still unclear. Experimental models with enforced oncogene expression in stem cells give rise to tumors infrequently when introduced into young progenitors, but at high rates when transplanted into old progenitors, or in young progenitors with an old cellular milieu. This finding indicates an interaction of intrinsic and extrinsic environments in transformation.[77] Similarly, when cancer-associated mutations are induced sequentially, the arising malignancy can be more aggressive if there is more time between the first and second mutation,[78] demonstrating a time-dependent, or environment-associated, effect on the type of malignancy.

In sum, cancer arising from stem cells is influenced by multiple factors, including the time needed to accumulate deleterious mutations. However, even when those mutations are present, additional factors, both genetic and environmental, are needed for transformation. This is a rich and relatively under-explored area that could lead to therapeutic approaches that reduce the risk of cancer.

Senescence. One of the challenges when reviewing literature on senescence is terminology. The term "senescence" is now commonly used to describe aging phenotypes, as opposed to the original meaning (which we will refer to as "replicative senescence"), which described the phenotype of irreversible cell cycle withdrawal[79] and the adoption of specific biochemical profiles.[80] This conflation is exemplified by the increasing use of the term "senescence" to refer to aging phenotypes of post-mitotic cells.[81,82] The absence of definitive markers of replicative senescent cells exacerbates this problem. A particular challenge is the characterization of rare stem cells or their progeny, but there is little evidence in any tissue that quiescent stem cells adopt senescent phenotypes without first entering the cell cycle. Furthermore, the ability to rejuvenate aged stem cell populations lends further support to the negligible amount of replicative senescence among aged stem cell populations.[1]

By contrast, the increased burden of senescent and inflammatory cells in the aging stem cell niche contributes to the overall inflammatory milieu.[1,83] Senescence and inflammation are inextricably linked when considering the biology of the aging stem cell niche.[83] Single-cell RNA-seq analysis of aged NSCs, MuSCs, and HSCs and their respective niches highlighted the prominent inflammation associated with age-related stem cell dysfunction.[84] In muscle, senescent cells in the niche impair aged MuSC function.[85] In NSCs, the increased inflammation is linked to interferon and CXCL10 signaling.[23,26] In the hippocampus, neuroblasts exhibit markers of the senescence-associated phenotype in the aging brain.[86] Aged skeletal stem cells not only respond to inflammatory signals with loss of function but also themselves contribute to the inflammatory milieu of the aged bone marrow.[87]

Altered resilience (survivability)

Cellular resilience describes the ability of a cell to deal with different forms of stress by inducing compensatory responses to maintain homeostasis. In the context of stem cell aging, we will focus primarily on the age-related loss of resilience that increases the likelihood of cell death in response to physiological or pathological stresses. Although not unique to stem cells, we include this among the hallmarks of stem cell aging because a

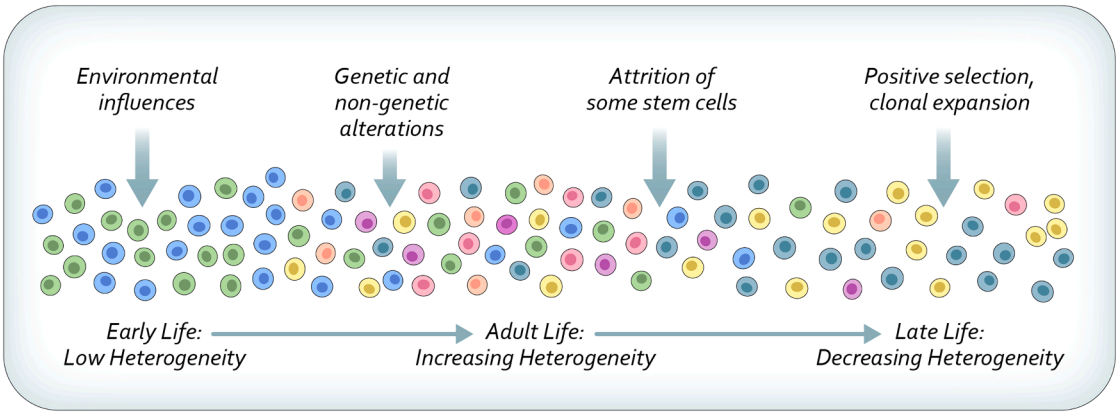

Figure 6. Changes in stem cell heterogeneity with age

The stem cell pool in most tissues is relatively homogeneous early in life, although there are discernable genetic distinctions and behaviors. Over time, the pool becomes more heterogeneous as cells acquire somatic mutations and experience different exposures to exogenous or endogenous stressors. They develop differences in epigenetic regulation, exhibit differences in mitochondrial function, and are influenced by all the hallmarks of aging. Ultimately, many stem cell pools then exhibit declining heterogeneity, as some stem cells are lost through attrition, and others survive or expand through positive selection. As the aging environment changes (e.g., systemic inflammation), some stem cells are more suited to that environment and expand, further reducing the heterogeneity of the pool. Mutations that cause cancer can be acquired at any time. The impact of these mutations on transformation can take decades to be observed, and additional alterations are usually required for transformation. A theoretical stem cell population corresponding to the hematopoietic system is illustrated, but the same process is acting in many other tissues.

decrease of resilience may contribute to the decline of a stem cell population over time, independently of changes in the other hallmarks. It may also account for an age-related decline in the outcome of key assays of stem cell function, such as transplantation. While the success of a stem cell transplantation experiment depends on features such as proliferative potential and self-renewal potential, the stem cells first need to survive the transplantation process. In that sense, resilience may be the primary characteristic that determines the success of stem cell transplantations.

In an early study of stem cell aging, age-related morphological changes in the mouse intestine were associated with a marked increase in stem cell apoptosis in response to low doses of irradiation.[88] This loss of resilience was associated with a decreased regenerative potential of aged ISCs, a defect that could be reversed by restoring Wnt signaling in aged ISCs back to youthful levels.[58]

In MuSCs, an age-related loss of resilience after reactivation from quiescence leads to a form of cell death known as mitotic catastrophe, in which cells die during mitosis.[89,90] This type of cell death is typically caused by unrepaired DNA lesions that interfere with the replicative machinery. With age, MuSCs exhibit a marked increase in mitotic catastrophe during a regenerative response, leading to a reduction of differentiated progeny and an even greater reduction of self-renewed MuSCs.[89] Consequently, the tissue responds less effectively to injuries because of a decline of the stem cell pool. The increase in mitotic catastrophe with age is caused by a decline in MuSC-mediated Notch signaling in the regenerative niche in a p53-dependent manner.[89]

In the hippocampus, *in vivo* imaging uncovered selective death of NSC progeny during aging in homeostatic conditions,[31] and it is likely that NSC death is further increased in response to injury in old brains. NSCs induce the activating transcription factor 4 (ATF4) pathway to promote survival associated with stresses of aging.[91] ATF4 is essential for maintaining the glutathione pool to protect NSCs from mitochondrial dysfunction.

Differences in resilience among variant HSC clones could account for some of the loss of heterogeneity in the hematopoietic system. Acquisition of mutations in protein phosphatase Mn^{2+}/Mg^{2+}-dependent 1D (PPM1D) and Snf2 related CREBBP activator protein (SRCAP) enhance the resistance of HSCs to environmental insults.[92,93] They show lower rates of apoptosis than other HSCs, which ultimately leads to their relative expansion in the HSC pool.

Interestingly, stem cell aging may also be associated with a gain of resilience. In mice, the age-related decline in hematopoiesis is due to the accumulation of dysfunctional HSCs that outcompete less resilient, functional HSCs.[94] This accumulation of dysfunctional HSCs, in turn, is driven by metabolic reprogramming. Through the increase of succinate dehydrogenase assembly factor 1 (SDHAF1) over time, HSCs become less dependent on glycolysis for ATP production and more resistant to oxidative stress.[94]

Changes in population heterogeneity

One stem cell hallmark that changes with age and can only be assessed with population studies is heterogeneity (Figure 6). As with other hallmarks included here, heterogeneity can either increase or decrease with age. Most cellular populations in the body show increased heterogeneity with age,[95] and this increase in heterogeneity is associated with a wide variety of causes, including accumulation of mutations in genomic and mitochondrial DNA, epigenetic changes, and loss of homeostatic mechanisms in processes such as autophagy, protein quality control, and RNA processing.[1,3,96–98] Likewise, stem cells exhibit an increase in genetic heterogeneity with age and they accumulate somatic mutations over time that give each stem cell a unique genetic fingerprint, which may affect its function.[99–101] This process can lead to increased heterogeneity in all of the functional

hallmarks described. In general, most stem cell populations exhibit a gradual increase in heterogeneity in functional assays during organismal aging. Aged HSCs exhibit a broader range of functionalities than young HSCs.[102] In the hippocampus, NSCs manifest increases in phenotypic and functional heterogeneity with aging, exhibiting marked changes in morphology.[103] NSCs in the SVZ are heterogeneous, both in terms of cellular transcriptome and spatial subregions, and this heterogeneity is linked to different progeny fates.[104,105] Single-cell RNA-seq studies have uncovered changes in NSC heterogeneity at the transcriptome during aging,[106,107] although it is unclear whether this leads to functional heterogeneity.

Paradoxically, the acquisition of genomic mutations can ultimately result in a decrease in stem cell population heterogeneity.[108] In the human hematopoietic system, this was established by examining peripheral blood production via deep sequencing and determining clonal contribution. In young individuals, thousands of stem cells are contributing to blood production at any given time. However, in aged individuals, there is a dramatic collapse, such that the majority of blood is being sustained by only a few clones.[109] The factors that lead to the collapse of heterogeneity are not well understood. Likely, a combination of attrition of some stem cells (caused by somatic mutations or accumulation of other age-related damage) and enhanced contributions of other stem cells due to the acquisition of somatic mutations (or possibly epimutations), which confer superior activity on these cells, are underlying causes. Some mutations, such as those affecting the *DNMT3A* gene, generally enhance stem cell fitness and result in incremental but steadily increased contributions to blood production over time,[110] whereas other mutations confer enhanced stem cell function primarily in an aged environment.[109] How these mutation lead to "super" stem cells is not completely understood, and likely varies among somatic mutations.[42] Experimentally, mutations in some epigenetic regulators, such as DNMT3A and TET2, enhance stem cell self-renewal, thus leading to a larger pool of HSCs that can disproportionately contribute to blood production. Many other genes, including genes in DNA damage response pathways, are also drivers of CH, and the consequences of these mutations likewise enhance the competitive advantage of those clones in ways distinct from epigenetic regulators.[92,93,111,112]

CH is not simply a marker of aging; it seems to contribute to multiple age-associated conditions. Several CH-associated genes are linked to hematologic disorders. Accordingly, the risk of developing hematologic malignancies is increased in the context of CH.[68,113] Importantly, CH is also associated with an elevated risk for some non-hematologic conditions, particularly cardiovascular disease. This is thought to be due to an increased inflammatory environment promoted by the large CH clones,[114–118] but detailed mechanisms are still unclear. CH has also been implicated in protection against some Alzheimer's pathologies,[116] and there is still more work needed to understand the broader effects on healthy aging.[116]

Age-associated clonal evolution that leads to loss of heterogeneity is evident in many tissues, for example, in human sun-exposed skin.[119] Among the genes that are commonly mutated (driving clonal expansions) are those in the Notch signaling cell pathway, a key driver of malignant transformation of skin cells in cancers, such as squamous cell carcinoma.[120] Similar clonal expansion associated with Notch (and other) mutations was observed the in epithelium of the esophagus.[121] Mutations in *TP53*, a critical tumor suppressor in most mammalian tissues, are also commonly found in expanded clones in many tissues. The prevalence of expanded clones with *TP53* and other mutations undoubtedly contribute to the increased rate of cancer with age.

In the intestine, the actively proliferating stem cells continuously compete for space within the stem cell niche in a process referred to as "neutral drift.[122,123]" This process can arise from cell competition driven by somatic mutations, but happens even in the absences of mutations, and results in a reduction of clonal heterogeneity with age. ISCs exhibit an age-related reduction in the expression of genes associated with cell adhesion, thus accelerating neutral drift.[124] Intriguingly, during homeostatic aging, MuSCs maintain clonal diversity, with loss of that diversity observed only in response to repeated bouts of muscle injury and regeneration.[125]

The accumulation of somatic mutations in tissues is universal, as DNA damage is constantly acquired even in post-mitotic tissue, and not all DNA is repaired perfectly; some mutations inevitably become fixed.[126] The extent to which accumulation of mutations per se contributes to aging, or just leads to altered stem cell and tissue function, is an important question for future studies.

INTERVENTIONS TO REJUVENATE AGED STEM CELLS

Features of stem cell aging provide an interesting contrast to the aging of other cells in the body, particularly post-mitotic cells. Whereas most, if not all, of the drivers of tissue aging are likely to affect stem cells as well, it may be that stem cells are uniquely resistant or uniquely sensitive to certain intrinsic and extrinsic stresses. Interventions that may delay or even reverse the impact of aging on cells and tissues receive considerable interest from scientific and lay communities alike. It is therefore interesting to consider how such interventions might target stem cells specifically. Within a framework of hallmarks of stem cell aging, the ability to rejuvenate aged stem cells may predict which interventions are likely to offer the greatest benefits for organismal health. Below, we highlight several interventions that have been studied in the context of stem cell aging and rejuvenation, although in most cases it is not possible to discern whether the beneficial effects arise from direct actions on stem cells or indirectly via the stem cell niches.

Systemic factors

Initial studies that modulated systemic factors to enhance aged stem cell function performed using heterochronic parabiosis and transfusion of young plasma into aged mice.[127] The initial heterochronic parabiosis studies of stem cell rejuvenation demonstrated enhanced function of aged MuSCs, improvements in survival, and cell fate changes.[59,128] These studies also suggested a change in the state of cellular quiescence, with an acceleration of quiescent MuSC entry into the cell cycle.[59,128] A subsequent study of NSCs revealed increased neurogenesis after transferring young plasma into old mice.[129] This increase most likely indicates a shallower depth of quiescence given the increased entry of NSCs into the cell cycle. Single-cell RNA-seq studies have

also confirmed the sensitivity of old NSCs to heterochronic parabiosis.[130] Over the years, many studies have revealed similar effects of young system factors on other aged stem/progenitor cell populations,[131] typically with an enhancement of proliferation or restoration of differentiation potential as the main readouts. Recently, single-cell RNA-seq analysis suggested that HSCs may be responsive to the rejuvenating effects of heterochronic parabiosis,[132] although there are conflicting data on this point.[133] The single-cell RNA-seq data supported the idea that youthful systemic factors revert the differentiation potential of aged HSC to that of younger animals.[132]

In addition to promoting rejuvenation with youthful systemic factors, approaches that block systemic pro-aging factors may be of value. A number of inflammatory cytokines increase with age that affect stem cell function.[41,129] Recently, interleukin-11 (IL-11) was found at high levels in the serum of aged mice, and blocking with an antibody ameliorated multiple aging-associated effects and extended lifespan.[134] The extent to which this has an effect on stem cell function remains to be determined.

CR/fasting

Among the most-studied dietary interventions with regard to aging benefits are caloric restriction (CR) and fasting.[135,136] CR is more complex because of the many variables (extent and duration of restriction, composition of the diet, etc.) that make comparisons of different studies challenging. HSCs from aged mice on 30% CR have demonstrated increased quiescence, resilience, and regenerative potential and a restoration of youthful differentiation trajectories.[137] The effects of CR on aged MuSCs is less clear, and both beneficial and detrimental effects have been reported.[138,139] In the intestine, CR increases ISC numbers by upregulating sirtuin, SIRT1, and promotes ISC differentiation via 3-hydroxy-3-methylglutaryl-coenzyme A synthetase 2 (HMGCS2).[140,141] In the brain, the effect of CR on NSCs is variable and may depend on the specific CR regimen and duration. For example, a 40% reduction in food intake for 6 months does not enhance proliferation of aged NSCs in the SVZ but does prevent the age-dependent decline in neurogenesis,[142] possibly by decreasing inflammation. Moreover, a 40% reduction in food intake for 12 months also prevents the age-dependent decrease in NSCs and their progenitors in the hippocampus.[143] However, intermittent fasting for 1 month is not sufficient to counter the age-dependent decline in NSCs in the hippocampus.[144] CR increases quiescence and the repopulation potential of aged HSCs and prevents the age-related increase of HSC numbers, while impairing differentiation along the lymphoid lineage.[145]

Fasting is somewhat more straightforward to study because the main variable is duration. A 24-h fast promotes intestinal regeneration in aged mice by enhancing the self-renewal potential of aged ISCs.[146] This beneficial effect is mediated by inducing a metabolic program of FAO in the ISCs, a process that is mediated by the rate limiting enzyme in FAO, Cpt1a.[146] Fasting benefits aged MuSCs as well. The induction of the ketone body β-hydroxy butyrate (BHB) in the serum by fasting enhances the resilience of MuSCs in aged mice.[147] This effect is due to a direct effect of BHB on MuSCs since *ex vivo* treatment leads to increased survival of aged MuSCs in transplantation studies.[147] Intermittent fasting restores youthful differentiation potential to aged oligodendrocyte progenitors (OPCs).[148] A regimen that mimics aspects of CR (intermittent fasting/re-feeding) leads to increased proliferation in the hippocampus, which may be due to the re-feeding phase.[149]

Exercise

Some of the earliest evidence of the benefits of exercise on the function of aged stem cells came from studies of neurogenesis. Voluntary wheel running increases the proliferation and survival of NSCs in the dentate gyrus.[150] Transfer of plasma from exercised mice to non-exercised mice likewise increases NSC proliferation,[151,152] suggesting that blood-borne factors mediate the effects of exercise on neurogenesis. Within the hematopoietic system, exercise increases HSC quiescence and reverses age-related changes in HSC differentiation potential, with corresponding changes in the transcriptome and epigenome.[153] With age, MuSCs exhibit a decrease in cyclin D1 expression and a corresponding slowing of activation out of quiescence.[154] Exercise restores youthful levels of cyclin D1 to aged MuSCs, enhances their activation, and promotes aged muscle repair. As with NSCs, transfer of plasma from exercised, aged mice to non-exercised aged mice increases cyclin D1 levels and youthful activation of aged MuSCs.[154] In a single-cell RNA-seq study of young and aged NSCs, MuSCs, and HSCs and their corresponding niches, exercise reverses age-related inflammatory signals in the niches and restores youthful molecular signatures in the stem cell compartments.[84] Both single-cell-specific aging clocks (machine learning models that predict age based on single-cell data) as well as spatial aging clocks (machine learning models that predict age based on spatial transcriptomic data) confirm the rejuvenating effect of exercise on the NSC lineage.[130,155]

Drug and metabolite treatments

A wide variety of drugs has been shown to slow the aging process, manifested as an extension of lifespan,[156] but few of these have been shown to exert their beneficial effects via actions on stem cells.. Among the many age-modifying drugs that have been studied, the few that have been tested in assays of stem cell function and tissue regeneration in aged animals include rapamycin and metformin.

Rapamycin, an inhibitor of mTOR, restores competitive repopulation activity to aged HSCs,[157] consistent with the increase in mTOR activity in HSCs with age. While there has been a lot of interest in the lay media for using rapamycin as a general anti-aging drug, not all the data are uniformly positive and side effects can be limiting.[158] Metformin, an activator of the AMPK pathway used in the treatment of type 2 diabetes, restores the molecular signature and differentiation potential of aged OPCs, thus enhancing remyelination in aged rats subjected to experimentally induced demyelination in the brain of aged rats.[148] Metformin also promotes NSC proliferation and self-renewal by increasing levels of the transcription factor Tap73, a member of the p53 family.[159]

Metformin has also been implicated in impacting CH, an intrinsically stem cell-driven aging phenomenon. Examination of samples from the UK Biobank showed that individuals taking metformin as an anti-diabetic treatment showed lower levels of *DNMT3A*-associated CH.[160] This result was linked to oxidative phosphorylation, and inhibition of mitochondrial electron

transport blocked the effects.[161] Moreover, a mouse model demonstrated that other drugs that blocked mitochondrial electron transport, such as MitoQ,[162] could also abrogate the effect of Dnmt3a-mutations on HSC expansion. The broader implications for aging are still unknown, but these studies point to an important role for metformin and mitochondria in HSC aging.

Several studies have shown that treatment of mice with a small molecule inhibitor of the RhoGTPase Cdc42 results in rejuvenation of different stem cell populations. This inhibitor, Cdc42 activity-specific inhibitor (CASIN), restores canonical Wnt signaling and youthful function in HFSCs.[163] Likewise, inhibition of Cdc42 enhances aged ISC function and restores crypt regeneration activity; Cdc42 also enhances HSC transplantation efficacy.[164,165] Pharmacological inhibition of Thrombospondin/CD47 signaling or enhancement of prostaglandin signaling both restore youthful function to aged MuSCs.[166,167]

In addition to drugs, metabolites that may mimic the effects of either diet or exercise have been tested in studies of improvements of aged stem cells. Nicotinamide riboside (NR), a precursor of NAD which declines with age,[168] restores ISC numbers in aged mice and reverses the age-related decline in ISC functions.[169] Likewise, NR supplementation increases HSC compartments in aged mice and improves survival after HSC transplantation by improving mitochondrial function.[170,171] Repletion of NAD with NR leads to variable enhancement of functions of MuSCs, NSCs, and McSCs.[172] The ability of metabolites to restore youthful function to aged stem cells is likely related to the key role these molecules play in determining the epigenetic status of cells as co-factors in epigenetic regulators.[173,174]

Partial reprogramming

There is much interest in the potential of partial reprogramming using Yamanaka factors (Oct3/4, Sox2, Klf4, and c-Myc [OSKM]) to restore youthful properties to aged cells throughout the body.[175] This approach to rejuvenation is based on the notion that the dedifferentiation potential can be uncoupled from the rejuvenation potential of OSKM factors.[176] The extent to which partial reprogramming impacts somatic stem cells, either directly or indirectly, has not been widely studied. Whole-body partial reprogramming enhances the regeneration of pancreas and muscle,[177] and more regional or cell-specific reprogramming enhances the regeneration of muscle and the regrowth of axons in the visual system after injuries.[178,179] However, in the cited studies there was no direct evidence of reprogramming of stem cells. Such whole-body reprogramming appeared to have negligible effects on middle-aged neural stem or progenitor cells in the hippocampus, but did enhance the migration of NSC progeny in both young and middle-aged mice.[180] In the SVZ, whole-body reprogramming as well as SVZ-targeted reprogramming could restore neural progenitor cell number and the generation of new neurons in the olfactory bulb.[181] Transient expression of reprogramming factors *in vitro* was shown to restore youthful properties to aged MuSCs from both mice and humans.[182]

CONCLUDING REMARKS

The field of stem cell aging has progressed rapidly and in parallel with remarkable advances in the broader field of the biology of aging.. The phenotypic characteristics of impaired regeneration of injured tissue in older individuals is now understood at the level of stem cell function and the environment in which those stem cells engage in tissue repair. Although this review has focused on the hallmarks of stem cell aging, age-related changes in the local and systemic environments and the immune system clearly play critical roles in all regenerative processes.

One of the challenges in the study of stem cell aging is the absence of a molecular definition of cellular age. Even as biomarkers, including various "aging clocks," are used to assess the biological age of somatic cells,[130,183] it is unclear how these record the age of the cell per se. Recent studies have revealed that stem cells may age at a different rate compared with the tissues in which they reside.[184] As such, it may be necessary to develop biomarkers of aging that are specific to the stem cell population under consideration and that may record differences in cellular age between differentiated cells and stem cells. Such an approach may be useful when developing aging interventions targeted toward stem cells that can replenish somatic tissues.

The absence of clear molecular determinants of cellular age makes it difficult to assess the aging of the cells and their "rejuvenation." As described above, there are many interventions and treatments that restore youthful properties to aged stem cells, but the extent to which any of these are true rejuvenations will depend on the molecular and functional characteristics that define a young stem cell. So far, a commonly used assessment for stem cell function across compartments is a stem cell's ability to proliferate and differentiate, which has been traditionally measured by incorporation of base analogs, lineage tracing, and marker analysis. Current challenges and opportunities in this area include the development of sophisticated *in vivo* imaging methods to visualize stem cell dynamic directly in a tissue[185,186] and artificial intelligence approaches. The emergence of artificial intelligence provides the opportunity to build foundation models for stem cells and more generalizable aging clocks, including spatial aging clocks,[155] or clocks based on modalities other than transcriptomics (e.g., proteomics, metabolomics, image-based, etc.). Such machine learning models, particularly if trained on stem cell function, should be particularly powerful at identifying rejuvenation approaches for stem cells across tissues and species.

Finally, as aged stem cells may be functionally enhanced without conversion back to a youthful molecular state, the molecular underpinnings of rejuvenation interventions, and the value of aging clocks in evaluating these interventions will be essential to understand. It will also be interesting to determine the durability of rejuvenating interventions, whether they can permanently enhance stem cell function, and the overall impact they have on the tissue and organism.

ACKNOWLEDGMENTS

The authors apologize for not including all relevant studies due to space constraints. They thank Dr. William Lowry and members of the Rando, Brunet, and Goodell laboratories for helpful comments. The authors thank Ms. Molly Thompson for her expertise and assistance with figure design and execution. This work was supported by a grant from the National Institutes of Health (National Institute on Aging; P01AG036695) to T.A.R., A.B., and M.A.G.

AUTHOR CONTRIBUTIONS

The authors contributed equally to all aspects of the article.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

1. Brunet, A., Goodell, M.A., and Rando, T.A. (2023). Ageing and rejuvenation of tissue stem cells and their niches. Nat. Rev. Mol. Cell Biol. *24*, 45–62. https://doi.org/10.1038/s41580-022-00510-w.

2. Rando, T.A., and Jones, D.L. (2021). Regeneration, rejuvenation, and replacement: Turning back the clock on tissue aging. Cold Spring Harb. Perspect. Biol. *13*, a040907. https://doi.org/10.1101/cshperspect.a040907.

3. Ermolaeva, M., Neri, F., Ori, A., and Rudolph, K.L. (2018). Cellular and epigenetic drivers of stem cell ageing. Nat. Rev. Mol. Cell Biol. *19*, 594–610. https://doi.org/10.1038/s41580-018-0020-3.

4. Liu, B., Qu, J., Zhang, W., Izpisua Belmonte, J.C., and Liu, G.H. (2022). A stem cell aging framework, from mechanisms to interventions. Cell Rep. *41*, 111451. https://doi.org/10.1016/j.celrep.2022.111451.

5. Fuchs, E., and Blau, H.M. (2020). Tissue stem cells: Architects of their niches. Cell Stem Cell *27*, 532–556. https://doi.org/10.1016/j.stem.2020.09.011.

6. López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., and Kroemer, G. (2023). Hallmarks of aging: An expanding universe. Cell *186*, 243–278. https://doi.org/10.1016/j.cell.2022.11.001.

7. Beumer, J., and Clevers, H. (2024). Hallmarks of stemness in mammalian tissues. Cell Stem Cell *31*, 7–24. https://doi.org/10.1016/j.stem.2023.12.006.

8. de Morree, A., and Rando, T.A. (2023). Regulation of adult stem cell quiescence and its functions in the maintenance of tissue integrity. Nat. Rev. Mol. Cell Biol. *24*, 334–354. https://doi.org/10.1038/s41580-022-00568-6.

9. Marescal, O., and Cheeseman, I.M. (2020). Cellular mechanisms and regulation of quiescence. Dev. Cell *55*, 259–271. https://doi.org/10.1016/j.devcel.2020.09.029.

10. Knobloch, M., Pilz, G.A., Ghesquière, B., Kovacs, W.J., Wegleiter, T., Moore, D.L., Hruzova, M., Zamboni, N., Carmeliet, P., and Jessberger, S. (2017). A fatty acid oxidation-dependent metabolic shift regulates adult neural stem cell activity. Cell Rep. *20*, 2144–2155. https://doi.org/10.1016/j.celrep.2017.08.029.

11. Ryall, J.G., Dell'orso, S., Derfoul, A., Juan, A., Zare, H., Feng, X., Clermont, D., Koulnis, M., Gutierrez-Cruz, G., Fulco, M., et al. (2015). The NAD(+)-dependent SIRT1 deacetylase translates a metabolic switch into regulatory epigenetics in skeletal muscle stem cells. Cell Stem Cell *16*, 171–183. https://doi.org/10.1016/j.stem.2014.12.004.

12. Capdevila, C., Miller, J., Cheng, L., Kornberg, A., George, J.J., Lee, H., Botella, T., Moon, C.S., Murray, J.W., Lam, S., et al. (2024). Time-resolved fate mapping identifies the intestinal upper crypt zone as an origin of Lgr5+ crypt base columnar cells. Cell *187*, 3039–3055.e14. https://doi.org/10.1016/j.cell.2024.05.001.

13. Malagola, E., Vasciaveo, A., Ochiai, Y., Kim, W., Zheng, B., Zanella, L., Wang, A.L.E., Middelhoff, M., Nienhüser, H., Deng, L., et al. (2024). Isthmus progenitor cells contribute to homeostatic cellular turnover and support regeneration following intestinal injury. Cell *187*, 3056–3071.e17. https://doi.org/10.1016/j.cell.2024.05.004.

14. Giangreco, A., Qin, M., Pintar, J.E., and Watt, F.M. (2008). Epidermal stem cells are retained in vivo throughout skin aging. Aging Cell *7*, 250–259. https://doi.org/10.1111/j.1474-9726.2008.00372.x.

15. Benjamin, D.I., Brett, J.O., Both, P., Benjamin, J.S., Ishak, H.L., Kang, J., Kim, S., Chung, M., Arjona, M., Nutter, C.W., et al. (2023). Multiomics reveals glutathione metabolism as a driver of bimodality during stem cell aging. Cell Metab. *35*, 472–486.e6. https://doi.org/10.1016/j.cmet.2023.02.001.

16. Chakkalakal, J.V., Jones, K.M., Basson, M.A., and Brack, A.S. (2012). The aged niche disrupts muscle stem cell quiescence. Nature *490*, 355–360. https://doi.org/10.1038/nature11438.

17. Rodgers, J.T., King, K.Y., Brett, J.O., Cromie, M.J., Charville, G.W., Maguire, K.K., Brunson, C., Mastey, N., Liu, L., Tsai, C.R., et al. (2014). mTORC1 controls the adaptive transition of quiescent stem cells from G0 to G(Alert). Nature *510*, 393–396. https://doi.org/10.1038/nature13255.

18. Haller, S., Kapuria, S., Riley, R.R., O'Leary, M.N., Schreiber, K.H., Andersen, J.K., Melov, S., Que, J., Rando, T.A., Rock, J., et al. (2017). mTORC1 activation during repeated regeneration impairs somatic stem cell maintenance. Cell Stem Cell *21*, 806–818.e5. https://doi.org/10.1016/j.stem.2017.11.008.

19. Dell'orso, S., Juan, A.H., Ko, K.D., Naz, F., Perovanovic, J., Gutierrez-Cruz, G., Feng, X., and Sartorelli, V. (2019). Single cell analysis of adult mouse skeletal muscle stem cells in homeostatic and regenerative conditions. Development *146*, dev174177. https://doi.org/10.1242/dev.174177.

20. Giordani, L., He, G.J., Negroni, E., Sakai, H., Law, J.Y.C., Siu, M.M., Wan, R., Corneau, A., Tajbakhsh, S., Cheung, T.H., et al. (2019). High-Dimensional Single-Cell Cartography Reveals Novel Skeletal Muscle-Resident Cell Populations. Mol. Cell *74*, 609–621.e6. https://doi.org/10.1016/j.molcel.2019.02.026.

21. Konagaya, Y., Rosenthal, D., Ratnayeke, N., Fan, Y., and Meyer, T. (2024). An intermediate Rb-E2F activity state safeguards proliferation commitment. Nature *631*, 424–431. https://doi.org/10.1038/s41586-024-07554-2.

22. Spencer, S.L., Cappell, S.D., Tsai, F.C., Overton, K.W., Wang, C.L., and Meyer, T. (2013). The proliferation-quiescence decision is controlled by a bifurcation in CDK2 activity at mitotic exit. Cell *155*, 369–383. https://doi.org/10.1016/j.cell.2013.08.062.

23. Kalamakis, G., Brüne, D., Ravichandran, S., Bolz, J., Fan, W., Ziebell, F., Stiehl, T., Catalá-Martinez, F., Kupke, J., Zhao, S., et al. (2019). Quiescence modulates stem cell maintenance and regenerative capacity in the aging brain. Cell *176*, 1407–1419.e14. https://doi.org/10.1016/j.cell.2019.01.040.

24. Bast, L., Calzolari, F., Strasser, M.K., Hasenauer, J., Theis, F.J., Ninkovic, J., and Marr, C. (2018). Increasing neural stem cell division asymmetry and quiescence are predicted to contribute to the age-related decline in neurogenesis. Cell Rep. *25*, 3231–3240.e8. https://doi.org/10.1016/j.celrep.2018.11.088.

25. Ibrayeva, A., Bay, M., Pu, E., Jörg, D.J., Peng, L., Jun, H., Zhang, N., Aaron, D., Lin, C., Resler, G., et al. (2021). Early stem cell aging in the mature brain. Cell Stem Cell *28*, 955–966.e7. https://doi.org/10.1016/j.stem.2021.03.018.

26. Dulken, B.W., Buckley, M.T., Navarro Negredo, P., Saligrama, N., Cayrol, R., Leeman, D.S., George, B.M., Boutet, S.C., Hebestreit, K., Pluvinage, J.V., et al. (2019). Single-cell analysis reveals T cell infiltration in old neurogenic niches. Nature *571*, 205–210. https://doi.org/10.1038/s41586-019-1362-5.

27. Ruetz, T.J., Pogson, A.N., Kashiwagi, C.M., Gagnon, S.D., Morton, B., Sun, E.D., Na, J., Yeo, R.W., Leeman, D.S., Morgens, D.W., et al. (2024). CRISPR-Cas9 screens reveal regulators of ageing in neural stem cells. Nature *634*, 1150–1159. https://doi.org/10.1038/s41586-024-07972-2.

28. Harris, L., Rigo, P., Stiehl, T., Gaber, Z.B., Austin, S.H.L., Masdeu, M.D.M., Edwards, A., Urbán, N., Marciniak-Czochra, A., and Guillemot, F. (2021). Coordinated changes in cellular behavior ensure the lifelong maintenance of the hippocampal stem cell population. Cell Stem Cell *28*, 863–876.e6. https://doi.org/10.1016/j.stem.2021.01.003.

29. Bottes, S., Jaeger, B.N., Pilz, G.A., Jörg, D.J., Cole, J.D., Kruse, M., Harris, L., Korobeynyk, V.I., Mallona, I., Helmchen, F., et al. (2021). Long-term self-renewing stem cells in the adult mouse hippocampus identified by intravital imaging. Nat. Neurosci. *24*, 225–233. https://doi.org/10.1038/s41593-020-00759-4.

30. Andersen, J., Urbán, N., Achimastou, A., Ito, A., Simic, M., Ullom, K., Martynoga, B., Lebel, M., Göritz, C., Frisén, J., et al. (2014). A transcriptional mechanism integrating inputs from extracellular signals to activate hippocampal stem cells. Neuron *83*, 1085–1097. https://doi.org/10.1016/j.neuron.2014.08.004.

31. Wu, Y., Bottes, S., Fisch, R., Zehnder, C., Cole, J.D., Pilz, G.A., Helmchen, F., Simons, B.D., and Jessberger, S. (2023). Chronic in vivo imaging defines age-dependent alterations of neurogenesis in the mouse hippocampus. Nat Aging *3*, 380–390. https://doi.org/10.1038/s43587-023-00370-9.

32. Comazzetto, S., Shen, B., and Morrison, S.J. (2021). Niches that regulate stem cells and hematopoiesis in adult bone marrow. Dev. Cell *56*, 1848–1860. https://doi.org/10.1016/j.devcel.2021.05.018.

33. Ding, L., Saunders, T.L., Enikolopov, G., and Morrison, S.J. (2012). Endothelial and perivascular cells maintain haematopoietic stem cells. Nature *481*, 457–462. https://doi.org/10.1038/nature10783.

34. Ding, L., and Morrison, S.J. (2013). Haematopoietic stem cells and early lymphoid progenitors occupy distinct bone marrow niches. Nature *495*, 231–235. https://doi.org/10.1038/nature11885.

35. Hammond, C.A., Wu, S.W., Wang, F., MacAldaz, M.E., and Eaves, C.J. (2023). Aging alters the cell cycle control and mitogenic signaling responses of human hematopoietic stem cells. Blood *141*, 1990–2002. https://doi.org/10.1182/blood.2022017174.

36. Post, Y., and Clevers, H. (2019). Defining adult stem cell function at its simplest: The ability to replace lost cells through mitosis. Cell Stem Cell *25*, 174–183. https://doi.org/10.1016/j.stem.2019.07.002.

37. Feige, P., Brun, C.E., Ritso, M., and Rudnicki, M.A. (2018). Orienting muscle stem cells for regeneration in homeostasis, aging, and disease. Cell Stem Cell *23*, 653–664. https://doi.org/10.1016/j.stem.2018.10.006.

38. Chambers, S.M., Shaw, C.A., Gatza, C., Fisk, C.J., Donehower, L.A., and Goodell, M.A. (2007). Aging hematopoietic stem cells decline in function and exhibit epigenetic dysregulation. PLoS Biol. *5*, e201. https://doi.org/10.1371/journal.pbio.0050201.

39. Sun, D., Luo, M., Jeong, M., Rodriguez, B., Xia, Z., Hannah, R., Wang, H., Le, T., Faull, K.F., Chen, R., et al. (2014). Epigenomic profiling of young and aged HSCs reveals concerted changes during aging that reinforce self-renewal. Cell Stem Cell *14*, 673–688. https://doi.org/10.1016/j.stem.2014.03.002.

40. de Haan, G., and Lazare, S.S. (2018). Aging of hematopoietic stem cells. Blood *131*, 479–487. https://doi.org/10.1182/blood-2017-06-746412.

41. Ergen, A.V., Boles, N.C., and Goodell, M.A. (2012). Rantes/Ccl5 influences hematopoietic stem cell subtypes and causes myeloid skewing. Blood *119*, 2500–2509. https://doi.org/10.1182/blood-2011-11-391730.

42. Challen, G.A., and Goodell, M.A. (2020). Clonal hematopoiesis: mechanisms driving dominance of stem cell clones. Blood *136*, 1590–1598. https://doi.org/10.1182/blood.2020006510.

43. Jaiswal, S., and Ebert, B.L. (2019). Clonal hematopoiesis in human aging and disease. Science *366*, eaan4673. https://doi.org/10.1126/science.aan4673.

44. Obernier, K., Cebrian-Silla, A., Thomson, M., Parraguez, J.I., Anderson, R., Guinto, C., Rodas Rodriguez, J., Garcia-Verdugo, J.M., and Alvarez-Buylla, A. (2018). Adult neurogenesis is sustained by symmetric self-renewal and differentiation. Cell Stem Cell *22*, 221–234.e8. https://doi.org/10.1016/j.stem.2018.01.003.

45. Tropepe, V., Craig, C.G., Morshead, C.M., and van der Kooy, D. (1997). Transforming growth factor-alpha null and senescent mice show decreased neural progenitor cell proliferation in the forebrain subependyma. J. Neurosci. *17*, 7850–7859. https://doi.org/10.1523/JNEUROSCI.17-20-07850.1997.

46. Nishino, J., Kim, I., Chada, K., and Morrison, S.J. (2008). Hmga2 promotes neural stem cell self-renewal in young but not old mice by reducing p16Ink4a and p19Arf Expression. Cell *135*, 227–239. https://doi.org/10.1016/j.cell.2008.09.017.

47. Molofsky, A.V., Slutsky, S.G., Joseph, N.M., He, S., Pardal, R., Krishnamurthy, J., Sharpless, N.E., and Morrison, S.J. (2006). Increasing p16INK4a expression decreases forebrain progenitors and neurogenesis during ageing. Nature *443*, 448–452. https://doi.org/10.1038/nature05091.

48. Gehart, H., and Clevers, H. (2019). Tales from the crypt: new insights into intestinal stem cells. Nat. Rev. Gastroenterol. Hepatol. *16*, 19–34. https://doi.org/10.1038/s41575-018-0081-y.

49. Huang, L., Bernink, J.H., Giladi, A., Krueger, D., van Son, G.J.F., Geurts, M.H., Busslinger, G., Lin, L., Begthel, H., Zandvliet, M., et al. (2024). Tuft cells act as regenerative stem cells in the human intestine. Nature *634*, 929–935. https://doi.org/10.1038/s41586-024-07952-6.

50. Blanpain, C., and Fuchs, E. (2014). Stem cell plasticity. Plasticity of epithelial stem cells in tissue regeneration. Science *344*, 1242281. https://doi.org/10.1126/science.1242281.

51. Sun, Q., Lee, W., Hu, H., Ogawa, T., De Leon, S., Katehis, I., Lim, C.H., Takeo, M., Cammer, M., Taketo, M.M., et al. (2023). Dedifferentiation maintains melanocyte stem cells in a dynamic niche. Nature *616*, 774–782. https://doi.org/10.1038/s41586-023-05960-6.

52. Dykstra, B., Kent, D., Bowie, M., McCaffrey, L., Hamilton, M., Lyons, K., Lee, S.J., Brinkman, R., and Eaves, C. (2007). Long-term propagation of distinct hematopoietic differentiation programs in vivo. Cell Stem Cell *1*, 218–229. https://doi.org/10.1016/j.stem.2007.05.015.

53. Beerman, I., Bhattacharya, D., Zandi, S., Sigvardsson, M., Weissman, I.L., Bryder, D., and Rossi, D.J. (2010). Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion. Proc. Natl. Acad. Sci. USA *107*, 5465–5470. https://doi.org/10.1073/pnas.1000834107.

54. Poscablo, D.M., Worthington, A.K., Smith-Berdan, S., Rommel, M.G.E., Manso, B.A., Adili, R., Mok, L., Reggiardo, R.E., Cool, T., Mogharrab, R., et al. (2024). An age-progressive platelet differentiation path from hematopoietic stem cells causes exacerbated thrombosis. Cell *187*, 3090–3107.e21. https://doi.org/10.1016/j.cell.2024.04.018.

55. Sanjuan-Pla, A., Macaulay, I.C., Jensen, C.T., Woll, P.S., Luis, T.C., Mead, A., Moore, S., Carella, C., Matsuoka, S., Bouriez Jones, T., et al. (2013). Platelet-biased stem cells reside at the apex of the haematopoietic stem-cell hierarchy. Nature *502*, 232–236. https://doi.org/10.1038/nature12495.

56. Encinas, J.M., Michurina, T.V., Peunova, N., Park, J.H., Tordo, J., Peterson, D.A., Fishell, G., Koulakov, A., and Enikolopov, G. (2011). Division-coupled astrocytic differentiation and age-related depletion of neural stem cells in the adult hippocampus. Cell Stem Cell *8*, 566–579. https://doi.org/10.1016/j.stem.2011.03.010.

57. Lee, S.W., Clemenson, G.D., and Gage, F.H. (2012). New neurons in an aged brain. Behav. Brain Res. *227*, 497–507. https://doi.org/10.1016/j.bbr.2011.10.009.

58. Nalapareddy, K., Nattamai, K.J., Kumar, R.S., Karns, R., Wikenheiser-Brokamp, K.A., Sampson, L.L., Mahe, M.M., Sundaram, N., Yacyshyn, M.B., Yacyshyn, B., et al. (2017). Canonical Wnt signaling ameliorates aging of intestinal stem cells. Cell Rep. *18*, 2608–2621. https://doi.org/10.1016/j.celrep.2017.02.056.

59. Brack, A.S., Conboy, M.J., Roy, S., Lee, M., Kuo, C.J., Keller, C., and Rando, T.A. (2007). Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science *317*, 807–810. https://doi.org/10.1126/science.1144090.

60. Stearns-Reider, K.M., D'Amore, A., Beezhold, K., Rothrauff, B., Cavalli, L., Wagner, W.R., Vorp, D.A., Tsamis, A., Shinde, S., Zhang, C., et al. (2017). Aging of the skeletal muscle extracellular matrix drives a stem cell fibrogenic conversion. Aging Cell *16*, 518–528. https://doi.org/10.1111/acel.12578.

61. Taylor-Jones, J.M., McGehee, R.E., Rando, T.A., Lecka-Czernik, B., Lipschitz, D.A., and Peterson, C.A. (2002). Activation of an adipogenic program in adult myoblasts with age. Mech. Ageing Dev. *123*, 649–661. https://doi.org/10.1016/s0047-6374(01)00411-0.

62. Bianco, P., Riminucci, M., Gronthos, S., and Robey, P.G. (2001). Bone marrow stromal stem cells: nature, biology, and potential applications. Stem Cells *19*, 180–192. https://doi.org/10.1634/stemcells.19-3-180.

63. Moerman, E.J., Teng, K., Lipschitz, D.A., and Lecka-Czernik, B. (2004). Aging activates adipogenic and suppresses osteogenic programs in mesenchymal marrow stroma/stem cells: the role of PPAR-gamma2 transcription factor and TGF-beta/BMP signaling pathways. Aging Cell *3*, 379–389. https://doi.org/10.1111/j.1474-9728.2004.00127.x.

64. Stolzing, A., Jones, E., McGonagle, D., and Scutt, A. (2008). Age-related changes in human bone marrow-derived mesenchymal stem

cells: consequences for cell therapies. Mech. Ageing Dev. *129*, 163–173. https://doi.org/10.1016/j.mad.2007.12.002.

65. Sui, B.D., Zheng, C.X., Li, M., Jin, Y., and Hu, C.H. (2020). Epigenetic regulation of mesenchymal stem cell homeostasis. Trends Cell Biol. *30*, 97–116. https://doi.org/10.1016/j.tcb.2019.11.006.

66. Butruille, L., Sébillot, A., Ávila, K., Vancamp, P., Demeneix, B.A., Pifferi, F., and Remaud, S. (2023). Increased oligodendrogenesis and myelination in the subventricular zone of aged mice and gray mouse lemurs. Stem Cell Rep. *18*, 534–554. https://doi.org/10.1016/j.stemcr.2022.12.015.

67. Tomasetti, C., and Vogelstein, B. (2015). Cancer etiology. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science *347*, 78–81. https://doi.org/10.1126/science.1260825.

68. Jaiswal, S., Fontanillas, P., Flannick, J., Manning, A., Grauman, P.V., Mar, B.G., Lindsley, R.C., Mermel, C.H., Burtt, N., Chavez, A., et al. (2014). Age-related clonal hematopoiesis associated with adverse outcomes. N. Engl. J. Med. *371*, 2488–2498. https://doi.org/10.1056/NEJMoa1408617.

69. Mayle, A., Yang, L., Rodriguez, B., Zhou, T., Chang, E., Curry, C.V., Challen, G.A., Li, W., Wheeler, D., Rebel, V.I., et al. (2015). Dnmt3a loss predisposes murine hematopoietic stem cells to malignant transformation. Blood *125*, 629–638. https://doi.org/10.1182/blood-2014-08-594648.

70. Challen, G.A., Sun, D., Jeong, M., Luo, M., Jelinek, J., Berg, J.S., Bock, C., Vasanthakumar, A., Gu, H., Xi, Y., et al. (2011). Dnmt3a is essential for hematopoietic stem cell differentiation. Nat. Genet. *44*, 23–31. https://doi.org/10.1038/ng.1009.

71. Chow, R.D., Velu, P., Deihimi, S., Belman, J., Youn, A., Shah, N., Luger, S.M., Carroll, M.P., Morrissette, J., and Bowman, R.L. (2025). Persistent postremission clonal hematopoiesis shapes the relapse trajectories of acute myeloid leukemia. Blood Adv. *9*, 1888–1899. https://doi.org/10.1182/bloodadvances.2024015149.

72. Wong, T.N., Ramsingh, G., Young, A.L., Miller, C.A., Touma, W., Welch, J.S., Lamprecht, T.L., Shen, D., Hundal, J., Fulton, R.S., et al. (2015). Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature *518*, 552–555. https://doi.org/10.1038/nature13968.

73. Jakobsen, N.A., Turkalj, S., Zeng, A.G.X., Stoilova, B., Metzner, M., Rahmig, S., Nagree, M.S., Shah, S., Moore, R., Usukhbayar, B., et al. (2024). Selective advantage of mutant stem cells in human clonal hematopoiesis is associated with attenuated response to inflammation and aging. Cell Stem Cell *31*, 1127–1144.e17. https://doi.org/10.1016/j.stem.2024.05.010.

74. Moore, L., Leongamornlert, D., Coorens, T.H.H., Sanders, M.A., Ellis, P., Dentro, S.C., Dawson, K.J., Butler, T., Rahbari, R., Mitchell, T.J., et al. (2020). The mutational landscape of normal human endometrial epithelium. Nature *580*, 640–646. https://doi.org/10.1038/s41586-020-2214-z.

75. Alcantara Llaguno, S., Chen, J., Kwon, C.H., Jackson, E.L., Li, Y., Burns, D.K., Alvarez-Buylla, A., and Parada, L.F. (2009). Malignant astrocytomas originate from neural stem/progenitor cells in a somatic tumor suppressor mouse model. Cancer Cell *15*, 45–56. https://doi.org/10.1016/j.ccr.2008.12.006.

76. Alcantara Llaguno, S.R., Wang, Z., Sun, D., Chen, J., Xu, J., Kim, E., Hatanpaa, K.J., Raisanen, J.M., Burns, D.K., Johnson, J.E., et al. (2015). Adult Lineage-Restricted CNS Progenitors Specify Distinct Glioblastoma Subtypes. Cancer Cell *28*, 429–440. https://doi.org/10.1016/j.ccell.2015.09.007.

77. Henry, C.J., Marusyk, A., Zaberezhnyy, V., Adane, B., and DeGregori, J. (2010). Declining lymphoid progenitor fitness promotes aging-associated leukemogenesis. Proc. Natl. Acad. Sci. USA *107*, 21713–21718. https://doi.org/10.1073/pnas.1005486107.

78. Loberg, M.A., Bell, R.K., Goodwin, L.O., Eudy, E., Miles, L.A., SanMiguel, J.M., Young, K., Bergstrom, D.E., Levine, R.L., Schneider, R.K., et al. (2019). Sequentially inducible mouse models reveal that Npm1 mutation causes malignant transformation of Dnmt3a-mutant clonal hematopoiesis. Leukemia *33*, 1635–1649. https://doi.org/10.1038/s41375-018-0368-6.

79. Hayflick, L., and Moorhead, P.S. (1961). The serial cultivation of human diploid cell strains. Exp. Cell Res. *25*, 585–621. https://doi.org/10.1016/0014-4827(61)90192-6.

80. Herranz, N., and Gil, J. (2018). Mechanisms and functions of cellular senescence. J. Clin. Invest. *128*, 1238–1246. https://doi.org/10.1172/JCI95148.

81. Herdy, J.R., Mertens, J., and Gage, F.H. (2024). Neuronal senescence may drive brain aging. Science *384*, 1404–1406. https://doi.org/10.1126/science.adi3450.

82. Redgrave, R.E., Dookun, E., Booth, L.K., Camacho Encina, M., Folaranmi, O., Tual-Chalot, S., Gill, J.H., Owens, W.A., Spyridopoulos, I., Passos, J.F., et al. (2023). Senescent cardiomyocytes contribute to cardiac dysfunction following myocardial infarction. NPJ Aging *9*, 15. https://doi.org/10.1038/s41514-023-00113-5.

83. Allen, N.C., Reyes, N.S., Lee, J.Y., and Peng, T. (2022). Intersection of inflammation and senescence in the aging lung stem cell niche. Front. Cell Dev. Biol. *10*, 932723. https://doi.org/10.3389/fcell.2022.932723.

84. Liu, L., Kim, S., Buckley, M.T., Reyes, J.M., Kang, J., Tian, L., Wang, M., Lieu, A., Mao, M., Rodriguez-Mateo, C., et al. (2023). Exercise reprograms the inflammatory landscape of multiple stem cell compartments during mammalian aging. Cell Stem Cell *30*, 689–705.e4. https://doi.org/10.1016/j.stem.2023.03.016.

85. Moiseeva, V., Cisneros, A., Sica, V., Deryagin, O., Lai, Y., Jung, S., Andrés, E., An, J., Segalés, J., Ortet, L., et al. (2023). Senescence atlas reveals an aged-like inflamed niche that blunts muscle regeneration. Nature *613*, 169–178. https://doi.org/10.1038/s41586-022-05535-x.

86. Jin, W.N., Shi, K., He, W., Sun, J.H., Van Kaer, L., Shi, F.D., and Liu, Q. (2021). Neuroblast senescence in the aged brain augments natural killer cell cytotoxicity leading to impaired neurogenesis and cognition. Nat. Neurosci. *24*, 61–73. https://doi.org/10.1038/s41593-020-00745-w.

87. Ambrosi, T.H., Marecic, O., McArdle, A., Sinha, R., Gulati, G.S., Tong, X., Wang, Y., Steininger, H.M., Hoover, M.Y., Koepke, L.S., et al. (2021). Aged skeletal stem cells generate an inflammatory degenerative niche. Nature *597*, 256–262. https://doi.org/10.1038/s41586-021-03795-7.

88. Martin, K., Potten, C.S., Roberts, S.A., and Kirkwood, T.B. (1998). Altered stem cell regeneration in irradiated intestinal crypts of senescent mice. J. Cell Sci. *111*, 2297–2303. https://doi.org/10.1242/jcs.111.16.2297.

89. Liu, L., Charville, G.W., Cheung, T.H., Yoo, B., Santos, P.J., Schroeder, M., and Rando, T.A. (2018). Impaired Notch signaling leads to a decrease in p53 activity and mitotic catastrophe in aged muscle stem cells. Cell Stem Cell *23*, 544–556.e4. https://doi.org/10.1016/j.stem.2018.08.019.

90. Castedo, M., Perfettini, J.L., Roumier, T., Andreau, K., Medema, R., and Kroemer, G. (2004). Cell death by mitotic catastrophe: a molecular definition. Oncogene *23*, 2825–2837. https://doi.org/10.1038/sj.onc.1207528.

91. Iqbal, M.A., Bilen, M., Liu, Y., Jabre, V., Fong, B.C., Chakroun, I., Paul, S., Chen, J., Wade, S., Kanaan, M., et al. (2024). The integrated stress response promotes neural stem cell survival under conditions of mitochondrial dysfunction in neurodegeneration. Aging Cell *23*, e14165. https://doi.org/10.1111/acel.14165.

92. Hsu, J.I., Dayaram, T., Tovy, A., De Braekeleer, E., Jeong, M., Wang, F., Zhang, J., Heffernan, T.P., Gera, S., Kovacs, J.J., et al. (2018). PPM1D mutations drive clonal hematopoiesis in response to cytotoxic chemotherapy. Cell Stem Cell *23*, 700–713.e6. https://doi.org/10.1016/j.stem.2018.10.004.

93. Chen, C.W., Zhang, L., Dutta, R., Niroula, A., Miller, P.G., Gibson, C.J., Bick, A.G., Reyes, J.M., Lee, Y.T., Tovy, A., et al. (2023). SRCAP mutations drive clonal hematopoiesis through epigenetic and DNA repair dysregulation. Cell Stem Cell *30*, 1503–1519.e8. https://doi.org/10.1016/j.stem.2023.09.011.

94. Watanuki, S., Kobayashi, H., Sugiura, Y., Yamamoto, M., Karigane, D., Shiroshita, K., Sorimachi, Y., Morikawa, T., Fujita, S., Shide, K., et al. (2024). SDHAF1 confers metabolic resilience to aging hematopoietic stem cells by promoting mitochondrial ATP production. Cell Stem Cell *31*, 1145–1161.e15. https://doi.org/10.1016/j.stem.2024.04.023.

95. Ferrucci, L., and Kuchel, G.A. (2021). Heterogeneity of aging: Individual risk factors, mechanisms, patient priorities, and outcomes. J. Am. Geriatr. Soc. *69*, 610–612. https://doi.org/10.1111/jgs.17011.

96. Kasbekar, M., Mitchell, C.A., Proven, M.A., and Passegué, E. (2023). Hematopoietic stem cells through the ages: A lifetime of adaptation to organismal demands. Cell Stem Cell *30*, 1403–1420. https://doi.org/10.1016/j.stem.2023.09.013.

97. Blau, H.M., Cosgrove, B.D., and Ho, A.T.V. (2015). The central role of muscle stem cells in regenerative failure with aging. Nat. Med. *21*, 854–862. https://doi.org/10.1038/nm.3918.

98. Keyes, B.E., and Fuchs, E. (2018). Stem cells: Aging and transcriptional fingerprints. J. Cell Biol. *217*, 79–92. https://doi.org/10.1083/jcb.201708099.

99. Goodell, M.A., Nguyen, H., and Shroyer, N. (2015). Somatic stem cell heterogeneity: diversity in the blood, skin and intestinal stem cell compartments. Nat. Rev. Mol. Cell Biol. *16*, 299–309. https://doi.org/10.1038/nrm3980.

100. Goodell, M.A., and Rando, T.A. (2015). Stem cells and healthy aging. Science *350*, 1199–1204. https://doi.org/10.1126/science.aab3388.

101. Haas, S., Trumpp, A., and Milsom, M.D. (2018). Causes and consequences of hematopoietic stem cell heterogeneity. Cell Stem Cell *22*, 627–638. https://doi.org/10.1016/j.stem.2018.04.003.

102. Yang, D., and de Haan, G. (2021). Inflammation and aging of hematopoietic stem cells in their niche. Cells *10*, 1849. https://doi.org/10.3390/cells10081849.

103. Martín-Suárez, S., Valero, J., Muro-García, T., and Encinas, J.M. (2019). Phenotypical and functional heterogeneity of neural stem cells in the aged hippocampus. Aging Cell *18*, e12958. https://doi.org/10.1111/acel.12958.

104. Alvarez-Buylla, A., Kohwi, M., Nguyen, T.M., and Merkle, F.T. (2008). The heterogeneity of adult neural stem cells and the emerging complexity of their niche. Cold Spring Harb. Symp. Quant. Biol. *73*, 357–365. https://doi.org/10.1101/sqb.2008.73.019.

105. Chaker, Z., Codega, P., and Doetsch, F. (2016). A mosaic world: puzzles revealed by adult neural stem cell heterogeneity. Wiley Interdiscip. Rev. Dev. Biol. *5*, 640–658. https://doi.org/10.1002/wdev.248.

106. Artegiani, B., Lyubimova, A., Muraro, M., van Es, J.H., van Oudenaarden, A., and Clevers, H. (2017). A single-cell RNA sequencing study reveals cellular and molecular dynamics of the hippocampal neurogenic niche. Cell Rep. *21*, 3271–3284. https://doi.org/10.1016/j.celrep.2017.11.050.

107. Xie, X.P., Laks, D.R., Sun, D., Poran, A., Laughney, A.M., Wang, Z., Sam, J., Belenguer, G., Fariñas, I., Elemento, O., et al. (2020). High-resolution mouse subventricular zone stem-cell niche transcriptome reveals features of lineage, anatomy, and aging. Proc. Natl. Acad. Sci. USA *117*, 31448–31458. https://doi.org/10.1073/pnas.2014389117.

108. Kapadia, C.D., and Goodell, M.A. (2024). Tissue mosaicism following stem cell aging: blood as an exemplar. Nat Aging *4*, 295–308. https://doi.org/10.1038/s43587-024-00589-0.

109. Mitchell, E., Spencer Chapman, M., Williams, N., Dawson, K.J., Mende, N., Calderbank, E.F., Jung, H., Mitchell, T., Coorens, T.H.H., Spencer, D. H., et al. (2022). Clonal dynamics of haematopoiesis across the human lifespan. Nature *606*, 343–350. https://doi.org/10.1038/s41586-022-04786-y.

110. Watson, C.J., Papula, A.L., Poon, G.Y.P., Wong, W.H., Young, A.L., Druley, T.E., Fisher, D.S., and Blundell, J.R. (2020). The evolutionary dynamics and fitness landscape of clonal hematopoiesis. Science *367*, 1449–1454. https://doi.org/10.1126/science.aay9333.

111. Kahn, J.D., Miller, P.G., Silver, A.J., Sellar, R.S., Bhatt, S., Gibson, C., McConkey, M., Adams, D., Mar, B., Mertins, P., et al. (2018). PPM1D-truncating mutations confer resistance to chemotherapy and sensitivity to PPM1D inhibition in hematopoietic cells. Blood *132*, 1095–1105. https://doi.org/10.1182/blood-2018-05-850339.

112. Miller, P.G., Sperling, A.S., Mayerhofer, C., McConkey, M.E., Ellegast, J. M., Da Silva, C., Cohen, D.N., Wang, C., Sharda, A., Yan, N., et al. (2023). PPM1D modulates hematopoietic cell fitness and response to DNA damage and is a therapeutic target in myeloid malignancy. Blood *142*, 2079–2091. https://doi.org/10.1182/blood.2023020331.

113. Genovese, G., Kähler, A.K., Handsaker, R.E., Lindberg, J., Rose, S.A., Bakhoum, S.F., Chambert, K., Mick, E., Neale, B.M., Fromer, M., et al. (2014). Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N. Engl. J. Med. *371*, 2477–2487. https://doi.org/10.1056/NEJMoa1409405.

114. Fuster, J.J., MacLauchlan, S., Zuriaga, M.A., Polackal, M.N., Ostriker, A. C., Chakraborty, R., Wu, C.L., Sano, S., Muralidharan, S., Rius, C., et al. (2017). Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science *355*, 842–847. https://doi.org/10.1126/science.aag1381.

115. Yura, Y., Miura-Yura, E., Katanasaka, Y., Min, K.D., Chavkin, N., Polizio, A.H., Ogawa, H., Horitani, K., Doviak, H., Evans, M.A., et al. (2021). The cancer therapy-related clonal hematopoiesis driver gene Ppm1d promotes inflammation and non-ischemic heart failure in mice. Circ. Res. *129*, 684–698. https://doi.org/10.1161/CIRCRESAHA.121.319314.

116. Bouzid, H., Belk, J.A., Jan, M., Qi, Y., Sarnowski, C., Wirth, S., Ma, L., Chrostek, M.R., Ahmad, H., Nachun, D., et al. (2023). Clonal hematopoiesis is associated with protection from Alzheimer's disease. Nat. Med. *29*, 1662–1670. https://doi.org/10.1038/s41591-023-02397-2.

117. Gajagowni, S., Hopkins, S., Qadeer, Y., Virani, S.S., Verdonschot, J.A.J., Coombs, C.C., Amos, C.I., Nead, K.T., Jaiswal, S., and Krittanawong, C. (2024). Clonal hematopoiesis of indeterminate potential and cardiovascular disease: Pathogenesis, clinical presentation, and future directions. Prog. Cardiovasc. Dis. *86*, 79–85. https://doi.org/10.1016/j.pcad.2024.09.001.

118. Jaiswal, S. (2020). Clonal hematopoiesis and nonhematologic disorders. Blood *136*, 1606–1614. https://doi.org/10.1182/blood.2019000989.

119. Martincorena, I., Roshan, A., Gerstung, M., Ellis, P., Van Loo, P., McLaren, S., Wedge, D.C., Fullam, A., Alexandrov, L.B., Tubio, J.M., et al. (2015). Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science *348*, 880–886. https://doi.org/10.1126/science.aaa6806.

120. Wang, N.J., Sanborn, Z., Arnett, K.L., Bayston, L.J., Liao, W., Proby, C. M., Leigh, I.M., Collisson, E.A., Gordon, P.B., Jakkula, L., et al. (2011). Loss-of-function mutations in Notch receptors in cutaneous and lung squamous cell carcinoma. Proc. Natl. Acad. Sci. USA *108*, 17761–17766. https://doi.org/10.1073/pnas.1114669108.

121. Martincorena, I., Fowler, J.C., Wabik, A., Lawson, A.R.J., Abascal, F., Hall, M.W.J., Cagan, A., Murai, K., Mahbubani, K., Stratton, M.R., et al. (2018). Somatic mutant clones colonize the human esophagus with age. Science *362*, 911–917. https://doi.org/10.1126/science.aau3879.

122. Snippert, H.J., van der Flier, L.G., Sato, T., van Es, J.H., van den Born, M., Kroon-Veenboer, C., Barker, N., Klein, A.M., van Rheenen, J., Simons, B. D., et al. (2010). Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell *143*, 134–144. https://doi.org/10.1016/j.cell.2010.09.016.

123. Lopez-Garcia, C., Klein, A.M., Simons, B.D., and Winton, D.J. (2010). Intestinal stem cell replacement follows a pattern of neutral drift. Science *330*, 822–825. https://doi.org/10.1126/science.1196236.

124. Hageb, A., Thalheim, T., Nattamai, K.J., Möhrle, B., Saçma, M., Sakk, V., Thielecke, L., Cornils, K., Grandy, C., Port, F., et al. (2022). Reduced adhesion of aged intestinal stem cells contributes to an accelerated clonal drift. Life Sci. Alliance *5*, e202201408. https://doi.org/10.26508/lsa.202201408.

125. Tierney, M.T., Stec, M.J., Rulands, S., Simons, B.D., and Sacco, A. (2018). Muscle stem cells exhibit distinct clonal dynamics in response to tissue repair and homeostatic aging. Cell Stem Cell *22*, 119–127.e3. https://doi.org/10.1016/j.stem.2017.11.009.

126. Cagan, A., Baez-Ortega, A., Brzozowska, N., Abascal, F., Coorens, T.H. H., Sanders, M.A., Lawson, A.R.J., Harvey, L.M.R., Bhosle, S., Jones, D., et al. (2022). Somatic mutation rates scale with lifespan across mammals. Nature *604*, 517–524. https://doi.org/10.1038/s41586-022-04618-z.

127. Conboy, I.M., and Rando, T.A. (2012). Heterochronic parabiosis for the study of the effects of aging on stem cells and their niches. Cell Cycle *11*, 2260–2267. https://doi.org/10.4161/cc.20437.

128. Conboy, I.M., Conboy, M.J., Wagers, A.J., Girma, E.R., Weissman, I.L., and Rando, T.A. (2005). Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature *433*, 760–764. https://doi.org/10.1038/nature03260.

129. Villeda, S.A., Luo, J., Mosher, K.I., Zou, B., Britschgi, M., Bieri, G., Stan, T.M., Fainberg, N., Ding, Z., Eggel, A., et al. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature *477*, 90–94. https://doi.org/10.1038/nature10357.

130. Buckley, M.T., Sun, E.D., George, B.M., Liu, L., Schaum, N., Xu, L., Reyes, J.M., Goodell, M.A., Weissman, I.L., Wyss-Coray, T., et al. (2023). Cell-type-specific aging clocks to quantify aging and rejuvenation in neurogenic regions of the brain. Nat Aging *3*, 121–137. https://doi.org/10.1038/s43587-022-00335-4.

131. Ashapkin, V.V., Kutueva, L.I., and Vanyushin, B.F. (2020). The effects of parabiosis on aging and age-related diseases. Adv. Exp. Med. Biol. *1260*, 107–122. https://doi.org/10.1007/978-3-030-42667-5_5.

132. Ma, S., Wang, S., Ye, Y., Ren, J., Chen, R., Li, W., Li, J., Zhao, L., Zhao, Q., Sun, G., et al. (2022). Heterochronic parabiosis induces stem cell revitalization and systemic rejuvenation across aged tissues. Cell Stem Cell *29*, 990–1005.e10. https://doi.org/10.1016/j.stem.2022.04.017.

133. Ho, T.T., Dellorusso, P.V., Verovskaya, E.V., Bakker, S.T., Flach, J., Smith, L.K., Ventura, P.B., Lansinger, O.M., Hérault, A., Zhang, S.Y., et al. (2021). Aged hematopoietic stem cells are refractory to bloodborne systemic rejuvenation interventions. J. Exp. Med. *218*, e20210223. https://doi.org/10.1084/jem.20210223.

134. Widjaja, A.A., Lim, W.W., Viswanathan, S., Chothani, S., Corden, B., Dasan, C.M., Goh, J.W.T., Lim, R., Singh, B.K., Tan, J., et al. (2024). Inhibition of IL-11 signalling extends mammalian healthspan and lifespan. Nature *632*, 157–165. https://doi.org/10.1038/s41586-024-07701-9.

135. Mazzoccoli, G., Tevy, M.F., Borghesan, M., Delle Vergini, M.R., and Vinciguerra, M. (2014). Caloric restriction and aging stem cells: the stick and the carrot? Exp. Gerontol. *50*, 137–148. https://doi.org/10.1016/j.exger.2013.10.014.

136. Mana, M.D., Kuo, E.Y.S., and Yilmaz, Ö.H. (2017). Dietary regulation of adult stem cells. Curr. Stem Cell Rep. *3*, 1–8. https://doi.org/10.1007/s40778-017-0072-x.

137. Tao, S., Wang, Y., Wu, J., Zeng, T., Cui, H., Tao, Z., Lei, L., Yu, L., Liu, A., Wang, H., et al. (2020). Long-term mid-onset dietary restriction rejuvenates hematopoietic stem cells and improves regeneration capacity of total bone marrow from aged mice. Aging Cell *19*, e13241. https://doi.org/10.1111/acel.13241.

138. Cerletti, M., Jang, Y.C., Finley, L.W.S., Haigis, M.C., and Wagers, A.J. (2012). Short-term calorie restriction enhances skeletal muscle stem cell function. Cell Stem Cell *10*, 515–519. https://doi.org/10.1016/j.stem.2012.04.002.

139. Boldrin, L., Ross, J.A., Whitmore, C., Doreste, B., Beaver, C., Eddaoudi, A., Pearce, D.J., and Morgan, J.E. (2017). The effect of calorie restriction on mouse skeletal muscle is sex, strain and time-dependent. Sci. Rep. *7*, 5160. https://doi.org/10.1038/s41598-017-04896-y.

140. Igarashi, M., and Guarente, L. (2016). mTORC1 and SIRT1 cooperate to foster expansion of gut adult stem cells during calorie restriction. Cell *166*, 436–450. https://doi.org/10.1016/j.cell.2016.05.044.

141. Gebert, N., Cheng, C.W., Kirkpatrick, J.M., Di Fraia, D., Yun, J., Schädel, P., Pace, S., Garside, G.B., Werz, O., Rudolph, K.L., et al. (2020). Region-specific proteome changes of the intestinal epithelium during aging and dietary restriction. Cell Rep. *31*, 107565. https://doi.org/10.1016/j.celrep.2020.107565.

142. Apple, D.M., Mahesula, S., Fonseca, R.S., Zhu, C., and Kokovay, E. (2019). Calorie restriction protects neural stem cells from age-related deficits in the subventricular zone. Aging *11*, 115–126. https://doi.org/10.18632/aging.101731.

143. Park, J.H., Glass, Z., Sayed, K., Michurina, T.V., Lazutkin, A., Mineyeva, O., Velmeshev, D., Ward, W.F., Richardson, A., and Enikolopov, G. (2013). Calorie restriction alleviates the age-related decrease in neural progenitor cell division in the aging brain. Eur. J. Neurosci. *37*, 1987–1993. https://doi.org/10.1111/ejn.12249.

144. Gabarró-Solanas, R., Davaatseren, A., Kleifeld, J., Kepčija, T., Köcher, T., Giralt, A., Crespo-Enríquez, I., and Urbán, N. (2023). Adult neural stem cells and neurogenesis are resilient to intermittent fasting. EMBO Rep. *24*, e57268. https://doi.org/10.15252/embr.202357268.

145. Tang, D., Tao, S., Chen, Z., Koliesnik, I.O., Calmes, P.G., Hoerr, V., Han, B., Gebert, N., Zörnig, M., Löffler, B., et al. (2016). Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging. J. Exp. Med. *213*, 535–553. https://doi.org/10.1084/jem.20151100.

146. Mihaylova, M.M., Cheng, C.W., Cao, A.Q., Tripathi, S., Mana, M.D., Bauer-Rowe, K.E., Abu-Remaileh, M., Clavain, L., Erdemir, A., Lewis, C.A., et al. (2018). Fasting activates fatty acid oxidation to enhance intestinal stem cell function during homeostasis and aging. Cell Stem Cell *22*, 769–778.e4. https://doi.org/10.1016/j.stem.2018.04.001.

147. Benjamin, D.I., Both, P., Benjamin, J.S., Nutter, C.W., Tan, J.H., Kang, J., Machado, L.A., Klein, J.D.D., de Morree, A., Kim, S., et al. (2022). Fasting induces a highly resilient deep quiescent state in muscle stem cells via ketone body signaling. Cell Metab. *34*, 902–918.e6. https://doi.org/10.1016/j.cmet.2022.04.012.

148. Neumann, B., Baror, R., Zhao, C., Segel, M., Dietmann, S., Rawji, K.S., Foerster, S., McClain, C.R., Chalut, K., van Wijngaarden, P., et al. (2019). Metformin restores CNS remyelination capacity by rejuvenating aged stem cells. Cell Stem Cell *25*, 473–485.e8. https://doi.org/10.1016/j.stem.2019.08.015.

149. Brandhorst, S., Choi, I.Y., Wei, M., Cheng, C.W., Sedrakyan, S., Navarrete, G., Dubeau, L., Yap, L.P., Park, R., Vinciguerra, M., et al. (2015). A periodic diet that mimics fasting promotes multi-system regeneration, enhanced cognitive performance, and healthspan. Cell Metab. *22*, 86–99. https://doi.org/10.1016/j.cmet.2015.05.012.

150. van Praag, H., Kempermann, G., and Gage, F.H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nat. Neurosci. *2*, 266–270. https://doi.org/10.1038/6368.

151. De Miguel, Z., Khoury, N., Betley, M.J., Lehallier, B., Willoughby, D., Olsson, N., Yang, A.C., Hahn, O., Lu, N., Vest, R.T., et al. (2021). Exercise plasma boosts memory and dampens brain inflammation via clusterin. Nature *600*, 494–499. https://doi.org/10.1038/s41586-021-04183-x.

152. Horowitz, A.M., Fan, X., Bieri, G., Smith, L.K., Sanchez-Diaz, C.I., Schroer, A.B., Gontier, G., Casaletto, K.B., Kramer, J.H., Williams, K.E., et al. (2020). Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. Science *369*, 167–173. https://doi.org/10.1126/science.aaw2622.

153. Frodermann, V., Rohde, D., Courties, G., Severe, N., Schloss, M.J., Amatullah, H., McAlpine, C.S., Cremer, S., Hoyer, F.F., Ji, F., et al. (2019). Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. Nat. Med. *25*, 1761–1771. https://doi.org/10.1038/s41591-019-0633-x.

154. Brett, J.O., Arjona, M., Ikeda, M., Quarta, M., de Morrée, A., Egner, I.M., Perandini, L.A., Ishak, H.D., Goshayeshi, A., Benjamin, D.I., et al. (2020). Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of Cyclin D1. Nat. Metab. *2*, 307–317. https://doi.org/10.1038/s42255-020-0190-0.

155. Sun, E.D., Zhou, O.Y., Hauptschein, M., Rappoport, N., Xu, L., Navarro Negredo, P., Liu, L., Rando, T.A., Zou, J., and Brunet, A. (2025). Spatial transcriptomic clocks reveal cell proximity effects in brain ageing. Nature *638*, 160–171. https://doi.org/10.1038/s41586-024-08334-8.

156. Nadon, N.L., Strong, R., Miller, R.A., and Harrison, D.E. (2017). NIA Interventions Testing Program: Investigating putative aging intervention agents in a genetically heterogeneous mouse model. EBioMedicine *21*, 3–4. https://doi.org/10.1016/j.ebiom.2016.11.038.

157. Chen, C., Liu, Y., Liu, Y., and Zheng, P. (2009). mTOR regulation and therapeutic rejuvenation of aging hematopoietic stem cells. Sci. Signal. *2*, ra75. https://doi.org/10.1126/scisignal.2000559.

158. Walters, H.E., and Cox, L.S. (2018). mTORC inhibitors as broad-spectrum therapeutics for age-related diseases. Int. J. Mol. Sci. *19*, 2325. https://doi.org/10.3390/ijms19082325.

159. Fatt, M., Hsu, K., He, L., Wondisford, F., Miller, F.D., Kaplan, D.R., and Wang, J. (2015). Metformin acts on two different molecular pathways

to enhance adult neural precursor proliferation/self-renewal and differentiation. Stem Cell Rep. *5*, 988–995. https://doi.org/10.1016/j.stemcr.2015.10.014.

160. Gozdecka, M., Dudek, M., Wen, S., Gu, M., Stopforth, R.J., Rak, J., Damaskou, A., Grice, G.L., McLoughlin, M.A., Bond, L., et al. (2025). Mitochondrial metabolism sustains DNMT3A-R882-mutant clonal haematopoiesis. Published online April 16, 2025. Nature. https://doi.org/10.1038/s41586-025-08980-6.

161. Hosseini, M., Voisin, V., Chegini, A., Varesi, A., Cathelin, S., Ayyathan, D. M., Liu, A.C.H., Yang, Y., Wang, V., Maher, A., et al. (2025). Metformin reduces the competitive advantage of Dnmt3a^{R878H} HSPCs. Published online April 16, 2025. Nature. https://doi.org/10.1038/s41586-025-08871-w.

162. Young, K.A., Hosseini, M., Mistry, J.J., Morganti, C., Mills, T.S., Cai, X., James, B.T., Nye, G.J., Fournier, N.R., Voisin, V., et al. (2025). Elevated mitochondrial membrane potential is a therapeutic vulnerability in Dnmt3a-mutant clonal hematopoiesis. Nat. Commun. *16*, 3306. https://doi.org/10.1038/s41467-025-57238-2.

163. Tiwari, R.L., Mishra, P., Martin, N., George, N.O., Sakk, V., Soller, K., Nalapareddy, K., Nattamai, K., Scharffetter-Kochanek, K., Florian, M.C., et al. (2021). A Wnt5a-Cdc42 axis controls aging and rejuvenation of hair-follicle stem cells. Aging *13*, 4778–4793. https://doi.org/10.18632/aging.202694.

164. Nalapareddy, K., Hassan, A., Sampson, L.L., Zheng, Y., and Geiger, H. (2021). Suppression of elevated Cdc42 activity promotes the regenerative potential of aged intestinal stem cells. iScience *24*, 102362. https://doi.org/10.1016/j.isci.2021.102362.

165. Montserrat-Vazquez, S., Ali, N.J., Matteini, F., Lozano, J., Zhaowei, T., Mejia-Ramirez, E., Marka, G., Vollmer, A., Soller, K., Sacma, M., et al. (2022). Transplanting rejuvenated blood stem cells extends lifespan of aged immunocompromised mice. NPJ Regen. Med. *7*, 78. https://doi.org/10.1038/s41536-022-00275-y.

166. Palla, A.R., Ravichandran, M., Wang, Y.X., Alexandrova, L., Yang, A.V., Kraft, P., Holbrook, C.A., Schürch, C.M., Ho, A.T.V., and Blau, H.M. (2021). Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength. Science *371*, eabc8059. https://doi.org/10.1126/science.abc8059.

167. Porpiglia, E., Mai, T., Kraft, P., Holbrook, C.A., de Morree, A., Gonzalez, V.D., Hilgendorf, K.I., Frésard, L., Trejo, A., Bhimaraju, S., et al. (2022). Elevated CD47 is a hallmark of dysfunctional aged muscle stem cells that can be targeted to augment regeneration. Cell Stem Cell *29*, 1653–1668.e8. https://doi.org/10.1016/j.stem.2022.10.009.

168. Johnson, S., and Imai, S.I. (2018). NAD^+ biosynthesis, aging, and disease. F1000Res *7*, 132. https://doi.org/10.12688/f1000research.12120.1.

169. Igarashi, M., Miura, M., Williams, E., Jaksch, F., Kadowaki, T., Yamauchi, T., and Guarente, L. (2019). NAD^+ supplementation rejuvenates aged gut adult stem cells. Aging Cell *18*, e12935. https://doi.org/10.1111/acel.12935.

170. Moon, J., Kim, H.R., and Shin, M.G. (2018). Rejuvenating aged hematopoietic stem cells through improvement of mitochondrial function. Ann. Lab. Med. *38*, 395–401. https://doi.org/10.3343/alm.2018.38.5.395.

171. Vannini, N., Campos, V., Girotra, M., Trachsel, V., Rojas-Sutterlin, S., Tratwal, J., Ragusa, S., Stefanidis, E., Ryu, D., Rainer, P.Y., et al. (2019). The NAD-booster nicotinamide riboside potently stimulates hematopoiesis through Increased mitochondrial clearance. Cell Stem Cell *24*, 405–418.e7. https://doi.org/10.1016/j.stem.2019.02.012.

172. Zhang, H., Ryu, D., Wu, Y., Gariani, K., Wang, X., Luan, P., D'Amico, D., Ropelle, E.R., Lutolf, M.P., Aebersold, R., et al. (2016). NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice. Science *352*, 1436–1443. https://doi.org/10.1126/science.aaf2693.

173. Brunet, A., and Rando, T.A. (2017). Interaction between epigenetic and metabolism in aging stem cells. Curr. Opin. Cell Biol. *45*, 1–7. https://doi.org/10.1016/j.ceb.2016.12.009.

174. Ren, R., Ocampo, A., Liu, G.H., and Izpisua Belmonte, J.C. (2017). Regulation of stem cell aging by metabolism and epigenetics. Cell Metab. *26*, 460–474. https://doi.org/10.1016/j.cmet.2017.07.019.

175. Roux, A.E., Zhang, C., Paw, J., Zavala-Solorio, J., Malahias, E., Vijay, T., Kolumam, G., Kenyon, C., and Kimmel, J.C. (2022). Diverse partial reprogramming strategies restore youthful gene expression and transiently suppress cell identity. Cell Syst. *13*, 574–587.e11. https://doi.org/10.1016/j.cels.2022.05.002.

176. Rando, T.A., and Chang, H.Y. (2012). Aging, rejuvenation, and epigenetic reprogramming: resetting the aging clock. Cell *148*, 46–57. https://doi.org/10.1016/j.cell.2012.01.003.

177. Ocampo, A., Reddy, P., Martinez-Redondo, P., Platero-Luengo, A., Hatanaka, F., Hishida, T., Li, M., Lam, D., Kurita, M., Beyret, E., et al. (2016). In vivo amelioration of age-associated hallmarks by partial reprogramming. Cell *167*, 1719–1733.e12. https://doi.org/10.1016/j.cell.2016.11.052.

178. Wang, C., Rabadan Ros, R., Martinez-Redondo, P., Ma, Z., Shi, L., Xue, Y., Guillen-Guillen, I., Huang, L., Hishida, T., Liao, H.K., et al. (2021). In vivo partial reprogramming of myofibers promotes muscle regeneration by remodeling the stem cell niche. Nat. Commun. *12*, 3094. https://doi.org/10.1038/s41467-021-23353-z.

179. Lu, Y., Brommer, B., Tian, X., Krishnan, A., Meer, M., Wang, C., Vera, D. L., Zeng, Q., Yu, D., Bonkowski, M.S., et al. (2020). Reprogramming to recover youthful epigenetic information and restore vision. Nature *588*, 124–129. https://doi.org/10.1038/s41586-020-2975-4.

180. Rodríguez-Matellán, A., Alcazar, N., Hernández, F., Serrano, M., and Ávila, J. (2020). In vivo reprogramming ameliorates aging features in dentate gyrus cells and improves memory in mice. Stem Cell Rep. *15*, 1056–1066. https://doi.org/10.1016/j.stemcr.2020.09.010.

181. Xu, L., Ramirez-Matias, J., Hauptschein, M., Sun, E.D., Lunger, J.C., Buckley, M.T., and Brunet, A. (2024). Restoration of neuronal progenitors by partial reprogramming in the aged neurogenic niche. Nat Aging *4*, 546–567. https://doi.org/10.1038/s43587-024-00594-3.

182. Sarkar, T.J., Quarta, M., Mukherjee, S., Colville, A., Paine, P., Doan, L., Tran, C.M., Chu, C.R., Horvath, S., Qi, L.S., et al. (2020). Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells. Nat. Commun. *11*, 1545. https://doi.org/10.1038/s41467-020-15174-3.

183. Oblak, L., van der Zaag, J., Higgins-Chen, A.T., Levine, M.E., and Boks, M.P. (2021). A systematic review of biological, social and environmental factors associated with epigenetic clock acceleration. Ageing Res. Rev. *69*, 101348. https://doi.org/10.1016/j.arr.2021.101348.

184. Gorelov, R., Weiner, A., Huebner, A., Yagi, M., Haghani, A., Brooke, R., Horvath, S., and Hochedlinger, K. (2024). Dissecting the impact of differentiation stage, replicative history, and cell type composition on epigenetic clocks. Stem Cell Rep. *19*, 1242–1254. https://doi.org/10.1016/j.stemcr.2024.07.009.

185. Pilz, G.A., Bottes, S., Betizeau, M., Jörg, D.J., Carta, S., April, S., Simons, B.D., Helmchen, F., and Jessberger, S. (2018). Live imaging of neurogenesis in the adult mouse hippocampus. Science *359*, 658–662. https://doi.org/10.1126/science.aao5056.

186. Gengatharan, A., Malvaut, S., Marymonchyk, A., Ghareghani, M., Snapyan, M., Fischer-Sternjak, J., Ninkovic, J., Götz, M., and Saghatelyan, A. (2021). Adult neural stem cell activation in mice is regulated by the day/night cycle and intracellular calcium dynamics. Cell *184*, 709–722.e13. https://doi.org/10.1016/j.cell.2020.12.026.