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Emerging models and paradigms for stem cell ageing

D. Leanne Jones and

Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, California 92037, USA

Thomas A. Rando

The Glenn Laboratories for the Biology of Aging and the Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford California 94305, USA, and the RR&D Center of Excellence and the Neurology Service, VAPAHCS, Palo Alto, California 94305, USA

Thomas A. Rando: rando@stanford.edu

Abstract

Ageing is accompanied by a progressive decline in stem cell function, resulting in less effective tissue homeostasis and repair. Here we discuss emerging invertebrate models that provide insights into molecular pathways of age-related stem cell dysfunction in mammals, and we present various paradigms of how stem cell functionality changes with age, including impaired self-renewal and aberrant differentiation potential.

As multicellular organisms age, there is a gradual loss of tissue homeostasis and organ function. Throughout life, populations of adult stem cells maintain many tissues, such as the blood, skin and intestinal epithelium. Therefore, it is likely that the decrease in tissue homeostasis can be attributed to an age-related decline in the ability of stem cells to replace damaged cells. Although cell autonomous changes occur as the organism ages that result in the inability of stem cells to proliferate or self-renew, or of daughter cells to differentiate along a specific lineage, local and systemic changes can also affect the ability of stem and progenitor cells to function properly.

A number of evolutionary theories attempt to provide a rationale for why we age and, ultimately, die (Box 1). Germline stem cells are probably subjected to different evolutionary pressures when compared with somatic stem cells given the very different roles the germline and soma play in the survival of species¹. However, ageing cannot be interpreted as simply a product of stem cell dysfunction. Likewise, longevity is not simply determined by the functionality of the tissues maintained by stem cells. Conditions such as neurodegeneration and cardiomyopathy are not thought to be consequences of somatic stem cell dysfunction. Furthermore, genotoxic and proteotoxic damage that accumulates in post-mitotic differentiated cells can also contribute to disease progression or lead to loss of tissue homeostasis, particularly when such cells provide a support function for tissue stem cells^{2–4}. Ultimately, understanding how and why we age must integrate mechanisms of both stem cell and post-mitotic cell ageing and the interplay between the two.

COMPETING FINANCIAL INTERESTS

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BOX 1**Evolutionary theory and stem cell ageing**

Many evolutionary theories have been proposed to explain the very existence of ageing of metazoans. They specifically try to reconcile the inexplicability — from an evolutionary perspective — of having a genetic ‘programme’ for ageing with the undeniable influence of genetics on longevity, and the phenotypes of ageing resulting from evolutionarily selected programmes for development, growth and adult homeostasis⁹⁸. The ‘disposable soma theory’ posits that selective pressures require a trade-off of resource utilization between somatic maintenance and reproduction. For example, to maximize reproductive success, organisms may have been selected to modulate the trade-off between somatic maintenance and reproduction based on environmental conditions, favouring reproduction during a time when resources are plentiful, but investing more in survival pathways and somatic maintenance when resources are scarce and reproductive success may be limited⁹⁹. Ageing is then the result of declining homeostatic mechanisms owing to inadequate investment in defence mechanisms to sustain an organism past the period of fertility. As stem cells contribute to somatic homeostasis, they will have been under similar selection pressures as the rest of the soma, and thus will have evolved differently to germline stem cells, despite their similarities.

An intriguing theory that may explain some features observed in aged stem cells is the ‘antagonistic pleiotropy’ theory, which posits that evolution selects for genes that are beneficial in early life even if they are detrimental later^{100,101}. p53 and mammalian target of rapamycin (mTOR) are notable examples of genes falling into this category^{1,102}. Many of the genes considered to exhibit antagonistic pleiotropy are tumour suppressors, beneficial by suppressing cancer early (and later) in life but potentially driving ageing by the very mechanisms by which they suppress cancer. The study of these genes with regard to age-related changes in stem cell function is important to understand how abnormal stem cell fate, including malignant transformation or senescence, can influence tissue ageing and, potentially, organismal longevity.

The interesting overlap between the biology of ageing and the biology of stem cells has been reviewed extensively^{3,5–8}. To the extent that stem cell ageing is itself an important factor in organismal ageing, it may be possible to develop therapeutic approaches to age-related diseases based on interventions to delay, prevent or even reverse stem cell ageing. Therefore, understanding the basic properties of stem cells as they age, and the mechanisms that promote or prevent stem cell ageing, have significant implications for regenerative medicine and the goal of extending ‘healthspan’. In this review, we highlight emerging model organisms that have begun to reveal general principles of stem cell ageing, and we present the emerging paradigms that characterize age-related decline in stem cell functionality.

Model organisms for the study of stem cell ageing

Much of what we know about genetic and environmental interventions and pathways that regulate longevity has come from studies in yeast (particularly the budding yeast, *Saccharomyces cerevisiae*) and invertebrate model organisms, such as *Caenorhabditis elegans* and *Drosophila melanogaster*^{9,10}. Although changes in longevity *per se* do not necessarily equate with changes in the ageing process, numerous genes and pathways identified in long-lived mutants have been shown to regulate cellular ageing. Mutations in

genes of the insulin/insulin-like growth factor signalling (IIS) pathway, the first genes identified to extend lifespan in worms^{11–13}, also seem to slow or delay the ageing process¹⁰.

Studies of effects of environmental interventions on the lifespan of model organisms have also revealed key genes and pathways for cellular ageing. Dietary restriction, defined as reduced calorific intake without malnutrition, is one of the most robust environmental interventions to extend lifespan^{14,15}, and both the IIS and the target of rapamycin (TOR) pathways have been implicated in mediating the effects of dietary restriction^{14–16}. Many of these pathways have now begun to emerge as important modulators of stem cell activity^{3,17–20}. Increasingly, genetic pathways that influence longevity in invertebrate organisms are being studied in the context of mammalian stem cell ageing.

S. cerevisiae

Replicative lifespan is the most widely studied aspect of ageing in *S. cerevisiae*²¹. With each division, the larger (mother) cell shows age-related changes and is able to give rise to a limited number of daughter cells. The number of such daughters defines the replicative lifespan and the process has features of the replicative lifespan of many dividing cells²², including stem cells. The sirtuin family of proteins, initially characterized by their effects on replicative lifespan in yeast²³, also influence cell and tissue ageing in metazoans²⁴.

In addition, budding yeast can be induced into a non-dividing stationary stage by the withdrawal of nutrients, and the cells then have a finite lifespan that has been studied as a model of organismal chronological ageing²⁵. Several features of yeast ageing are relevant to general phenomena linked to stem cell ageing. Budding itself is a model for stem cell self-renewal, as two cells are produced in an asymmetric cell division, ensuring continual self-renewal of a mother cell. Furthermore, the ability of the daughter to maintain a youthful state by limiting its inheritance of damaged macromolecules can be considered as a model for germline stem cell function²⁶.

C. elegans

In contrast to the continually dividing budding yeast, the adult stage of *C. elegans* is composed entirely of post-mitotic cells, with the exception of a population of highly proliferative germline stem cells (GSCs). Studies of *C. elegans* longevity have revealed intriguing relationships between the GSCs and lifespan. An inextricable link between ageing and the germline is demonstrated by the fact that ablation of the germline, but not the entire gonad, leads to lifespan extension in worms^{27,28}. Furthermore, recent studies have demonstrated that factors involved in epigenetic regulation of gene expression, such as ASH-2 and RBR-2 (a histone methyltransferase and a histone demethylase, respectively), influence lifespan in a germline-dependent manner²⁹. Interestingly, nematodes in which GSCs have been ablated or carry mutations that disrupt their maintenance, display a decrease in overall lipid stores, caused by upregulation of an intestinal triglyceride lipase, resulting in leaner and long-lived animals³⁰.

Drosophila

Similarly to yeast and *C. elegans*, *Drosophila* offers a tractable genetic system that is invaluable for exploring the genetic regulation of lifespan³¹, and also offers the unique advantage of having a number of tissues in the adult that are maintained by resident stem cells. Adult stem cells in *Drosophila*, such as GSCs in the ovary and the testis and the intestinal stem cells (ISCs) in the midgut, reside in defined niches and have active roles in maintaining local tissue homeostasis, similar to their mammalian counterparts³². Furthermore, additional stem-cell-like compartments in *Drosophila* are only just beginning

to be identified and may also turn out to be useful models for stem cell function and regulation^{33–35}.

In both the ovary and testis, GSCs reside within a well-characterized niche at the tip of the gonads³⁶, where they are adjacent to support cells that secrete essential self-renewal and maintenance signals. GSCs in both males and females divide asymmetrically to give rise to a daughter stem cell and a progenitor cell that will undergo a series of mitotic amplification divisions before the onset of terminal differentiation to generate mature gametes³⁶.

Multipotent intestinal stem cells (ISCs), the only proliferating cells in the midgut, are distributed along the basement membrane^{37,38}. The circular muscles underlying the gut produce the ligand Wingless (Wg) to activate the Wnt signalling pathway in ISCs, and have been proposed as the niche that promotes ISC self-renewal³⁹. ISCs divide to give rise to one stem cell and a cell that becomes an enteroblast. Enteroblasts do not divide again and differentiate into small diploid enteroendocrine cells or large polyploid enterocytes^{37,38}. Both ISCs and enteroblasts express the transcription factor escargot (esg), which is often used as a surrogate marker for ISCs and enteroblasts. Furthermore, the ligand Delta (Dl) specifically accumulates in ISCs, but it is quickly lost in newly formed enteroblasts as Notch signalling is activated and differentiation initiated^{37,38}.

By using the information regarding the homeostatic state of stem cells in various *Drosophila* tissues and dissecting the mechanisms that seem to influence stem cell ageing in mammals, such as the interaction between stem cells and their niches, we should be able to increase our understanding of the concepts behind these processes in other organisms, including humans. Emerging from studies of the ageing of stem cells in both invertebrate model organisms and mammalian systems are paradigms that characterize the functional changes that occur as stem cells age. From studies of interventions, genetic or environmental, that alter cellular or organismal ageing, information about the key factors that influence stem cell function is also gathered. These factors range from local and systemic signals, pathways that transmit those signals into the stem cell cytoplasm and nucleus, to the identification of intracellular targets of signalling (such as DNA, proteins and mitochondria) that may be the effectors of age-related changes in stem cell function. In the following sections, we will first provide a framework for considering the various paradigms of stem cell ageing that have been characterized (Fig. 1), and we will also highlight potential targets and effectors responsible for those age-related changes.

Functional characteristics of stem cell ageing

Although not mutually exclusive, several distinct processes have been characterized that distinguish the functional properties of aged stem cells from their younger counterparts. Each induces a decline in stem cell functionality in some way, and several, but not all, result in a change in stem cell number with age (Box 2). We present examples in which the age-related changes have been well documented.

BOX 2

Ageing and stem cell numbers

It might be supposed that, with age, there is an overall decline in stem cell number and that we ultimately die because we simply run out of stem cells. However, that is certainly not the case. For vital systems, there is more than enough stem cell potential. This is most clearly demonstrated by serial transplantation of HSCs that can sustain mice across multiple lifespans¹⁰³. Where stem cell numbers have been measured, whether there is a sustained number, a decline or even an increase depends on the specific tissue and species, and even the strain. In the mouse, HSCs increase with age in some, but not all

strains¹⁰⁴. Likewise, in mammalian muscle, the number of MuSCs seems to be relatively constant with age, but may either increase or decrease depending on the specific muscle examined and the method used for quantification¹⁰⁵. Ageing in the *Drosophila* midgut is characterized by an increase in the percentage of proliferative ISCs^{64,65}. However, there are also clear examples of tissues in which stem cells do decline with age. In mammals, this is the case for NSCs, melanocyte stem cells and spermatogonial stem cells^{40–42,106,107}. Likewise, in *Drosophila*, a decline in gametogenesis in ageing males and females is due, in part, to a decrease in the average number of GSCs^{43–45}. Although the loss of stem cells in each of these specific tissues clearly has functional implications for that tissue, there is no evidence that it results in a reduction in lifespan. In short, generalizations about age-related changes in stem cell number are not possible, and each tissue must be analysed individually in each species.

Failure of self-renewal

Failure of self-renewal of stem cells with age (Fig. 1b) occurs in some stem cell compartments and is one process that may result in an age-related decline in stem cell number. The number of stem cells contributing to neurogenesis in the mammalian brain and skin pigmentation declines with age^{40,41}. Rather than undergoing asymmetric cell divisions to yield differentiated progeny and new stem cells, these cells increasingly generate progeny that do not maintain the stem cell pool. In the neural stem cell (NSC) compartment, stem cell self-renewal is regulated by the FoxO family of transcription factors^{40,42}, which are components of the IIS pathway. In the melanocyte stem cell pool, failure of self-renewal may be the result of premature differentiation owing to sensitivity to DNA damage⁴¹.

In the fly, oogenesis and spermatogenesis rapidly decline with age, correlating with a significant decrease in GSC number and a decline of the self-renewal ability of the remaining GSCs^{43–45}. This gradual loss can be attributed to a decrease in expression of self-renewal factors expressed by local support cells, as well as a reduction in cell–cell adhesion molecules that normally hold stem cells within the niche and close to self-renewal signals^{44,45}. Re-expression of self-renewal factors in niche support cells or of the *Drosophila* E-cadherin in GSCs was shown to be sufficient to suppress GSC loss in aged flies^{44,45}. However, in aged males, maintenance of self-renewal signals was not sufficient to restore proliferation of GSCs to the level observed in young males, indicating that additional changes affect stem cell ageing in this system^{44,46}. In aged flies, slower GSC proliferation also contributes to decreased gametogenesis^{44–48}. Consistent with these observations, mispositioned centrosomes were frequently observed in GSCs in aged males and could induce a delay or arrest in cell cycle progression^{44,46}.

Decline of extrinsic signals or responsiveness to those signals

An age-related decline in tissue homeostasis or regenerative potential may result from a decreased intrinsic responsiveness of the stem cells or a decrease in the environmental signals (Fig. 1b). Mammalian muscle stem cells (MuSCs; also known as ‘satellite cells’) exhibit a relatively low responsiveness to extrinsic stimuli as the organism ages, resulting in decreased activation, proliferation and regenerative response^{49,50}. This is due in part to changes in their niche, which for MuSCs is the adjacent myofibre in close apposition². Aged muscle myofibres express lower levels of the Notch ligand Delta-like 1, which is necessary for stem cell activation^{51,52}. Heterochronic transplantation studies in which young cells are placed into an old host (or *vice versa*) had suggested that the decreased responsiveness was due to the aged environment rather than changes intrinsic to the MuSCs themselves⁵³. Heterochronic parabiotic studies — in which aged mice are surgically connected to young mice such that each pair develops a single shared circulatory system, allowing young stem

cells to be exposed to an aged systemic milieu and *vice versa* — have confirmed the importance of environmental influences on MuSC function with age^{50,52}. These studies have demonstrated unequivocally that stem cell function is strongly influenced by systemic factors and that aged stem cells can be rejuvenated by exposure to a youthful environment⁵², highlighting the reversibility of some cell-intrinsic changes responsible for age-related stem cell dysfunction⁵⁴. Likewise, the aged environment influences young stem cells to adopt a more aged phenotype⁵⁰. Thus, in muscle, both local and systemic environment participate in determining the functional capacity of stem cells with age.

In aged flies, systemic factors, including *Drosophila* insulin-like peptides (dILPs), have also been demonstrated to influence GSC proliferation and maintenance through autonomous and non-autonomous mechanisms in males and females^{3,55–58}. A decline in IIS signalling has been reported in the ovary from aged females⁵⁶. Therefore, age-related changes in expression of circulating or locally expressed dILPs could also contribute to the decline in *Drosophila* GSC number and activity during ageing.

Abnormal progenitor differentiation

For normal tissue homeostasis and regeneration, stem cells must give rise to the appropriate number and types of differentiated progeny. Examples of age-related changes in this critical property include excessive proliferation of one type of progenitor, skewed distribution of progeny among normal fates and aberrant differentiation to abnormal fates (Fig. 1b).

Aged murine MuSCs exhibit a propensity to diverge from the myogenic lineage and adopt a fibrogenic fate, a property that contributes to impaired regeneration and promotes increased fibrosis⁵⁰. *In vivo* and *in vitro* studies of MuSCs show that the Wnt pathway is more active in older MuSCs and induces this cell fate change⁵⁰. MuSCs treated with Wnt agonists or aged serum are diverted from myogenic differentiation towards the fibrogenic lineage, but depletion of Wnt-inducing activity from aged serum abrogates the effect⁵⁰. It was further found that local production of TGF- β (transforming growth factor β) within the MuSC niche increases with age and suppresses satellite cell function⁵⁹.

Aged murine haematopoietic stem cells (HSCs) exhibit a skewed differentiation potential toward the myeloid lineage⁶⁰, resulting in a decreased immune response and a predisposition to develop myeloid leukaemia. HSCs isolated from aged mice display a decrease in expression of genes correlated with lymphoid differentiation with a concomitant increase in genes associated with myeloid fate and leukaemogenesis⁶⁰. Ageing seems to result in the clonal expansion of a subset of HSCs biased to adopt a myeloid fate, rather than to a more global change in gene expression throughout a homogeneous HSC population^{61–63}.

In the *Drosophila* midgut, a marked age-dependent increase in ISC proliferation can be observed and is accompanied by accumulation of misdifferentiated daughter cells, expressing markers of both ISCs (such as *esg* and *DI*) and of terminally differentiated cells^{64–66}. As these cells retain expression of the stem cell and are polyploid, they resemble enteroblasts but have lost their ability to terminally differentiate into functional enterocytes^{64–66}. Defective differentiation leads to loss of tissue homeostasis and severe deterioration of the midgut epithelium in aged flies^{58,65}. A similar phenotype is observed when the gut epithelium is exposed to oxidative stress, tissue-damaging agents, enteric bacterial infections or direct ablation of enterocytes through apoptosis, all of which promote compensatory ISC division and an increase in misdifferentiating progenitor cells^{64,65,67–69}. It is possible that chronic exposure to these environmental factors could contribute to changes in ISC activity in ageing flies.

IIS activity is also required for ISC proliferation and may have a role in the proliferative response of ISCs to ageing and tissue damage^{68,70}. dILP-expressing cells in the fly brain influence ISC proliferation and age-related dysplasia^{68,70}. Moderate reduction of IIS activity in ISCs/enteroblasts is sufficient to limit ISC proliferation and promote homeostasis⁷⁰. Ageing of muscle in *Drosophila* is modulated by the transcription factor dFoxO, which is negatively regulated downstream of the IIS pathway^{71,72}. Given that the circular muscle is a likely component of the ISC niche and a source of factors that promote ISC proliferation⁷³, age-related changes in IIS could also affect ISC activity through the niche. Interestingly, delaying age-related changes in the midgut, by modulating IIS activity, extends lifespan⁷⁰. Whether this intervention delays ageing in other tissues is unclear but this result provides a foundation to begin exploring if counteracting the effects of ageing in one stem cell population could affect other tissues, possibly through systemic factors.

Senescence and apoptosis

In addition to aberrant differentiation, it is unclear if changes in stem cell functionality with age are due to either senescence or apoptosis (Fig. 1d). Cellular senescence is characterized by irreversible cell cycle arrest and the secretion of factors that may negatively impact surrounding cells⁷⁴. It increases with age in some mammalian tissues, but it is unclear how prevalent this process is and how much it contributes to tissue ageing. Senescence of adult stem cells has not been clearly demonstrated but indirect evidence suggests that signalling pathways associated with cellular senescence increase with age in some stem cell compartments⁶. A mutant mouse strain deficient in Klotho, a protein known to be involved in mineral homeostasis, and that when absent leads to a progeroid syndrome^{75,76}, exhibits features of elevated Wnt signalling that may lead to senescence of stem cells in the skin and gut⁷⁷. Such cells exhibit foci of γ -H2AX staining that are characteristic of senescence induction by DNA damage⁷⁸. Likewise, aged HSCs and MuSCs exhibit high levels of γ -H2AX foci^{79,80}. As DNA damage may also lead to apoptosis, the presence of these foci may reveal stem cells on the path to death as opposed to senescence. However, as with senescence, stem cell apoptosis has not been demonstrated to be a feature of normal ageing. Nevertheless, low levels of apoptosis occurring during normal ageing could be difficult to detect and easily overlooked.

Cell intrinsic targets and mediators of stem cells ageing

In the previous section, we have described the ways in which aged stem cells differ in functional responses from their younger counterparts. Several evolutionarily conserved signalling pathways, such as the IIS, TOR and Wnt pathways contribute to age-related changes in stem cell functionality. However, in most cases, or most of the specific paradigms described, the exact intracellular signalling pathways and responses that result in the aged stem cell properties are not known. In the following sections, we present cell-intrinsic changes that have been measured in aged stem cells and may determine the functionality of aged stem cells.

Changes in transcriptional and epigenetic regulators

Transcriptional profiling revealed that genes associated with chronic inflammation, stress and proteotoxicity were upregulated in HSCs isolated from old mice, whereas genes associated with genomic integrity (also see below) and chromatin remodelling were downregulated⁸¹. Profiling of NSCs from fetal and aged mice showed a similar age-related decline in expression of a chromatin-remodelling factor, Hmga2 (ref. 82), partly owing to let7b-mediated microRNA degradation, which leads to increased expression of the tumour suppressors p16 (Ink4a) and p19 (Arf) and thus contributes to NSC proliferation decline⁸². Increased p16 expression has been observed in a number of other tissues, including HSCs,

lymphoid progenitors and pancreatic β -cells, and has been proposed to be a biomarker of human ageing^{83–86}. Studies in humans show the association of polymorphisms near the p16 and p19 loci with an increased incidence of age-related pathologies⁶. Therefore, increases in p16 with age, even if potentially suppressing stem cell function (Box 1), might actually be essential to limit age-related diseases.

Genomic instability

The extent to which irreversible changes within the genome negatively affect stem cell ageing is also an active area of investigation. Many genetic mutations that cause progerias lead to genomic instability, which both shortens lifespan and negatively affects stem cell function (Box 3). However, in the absence of such mutations, the role of genomic instability in normal age-related stem cell changes remains to be determined. Markers of DNA damage, perhaps reflecting genomic instability, have been reported in populations of aged stem cells^{79,80}. Recent studies highlight the different strategies by stem and progenitor cells in response to DNA damage, as well as differences in responses in human and murine systems⁸⁷. Furthermore, a vigilant DNA damage repair system is important for protecting bulge stem cells from cell death⁸⁸. Telomere shortening can trigger a DNA damage response and has been reported in highly proliferative ageing tissues⁸⁹, although the status of telomeres in purified stem cell populations is less well defined⁹⁰. Furthermore, genotoxic stress on stem cells niche components also indirectly compromise tissue homeostasis and requires further characterization. For example, loss of telomerase activity affects lymphopoiesis in a non-cell autonomous manner^{91,92}. As adult stem cells may have unique features that limit the acquisition of mutations over a lifetime⁸⁰, stringent tests are needed to determine whether enhancing DNA repair or maintaining telomere length could prevent age-related decline in stem cell function.

BOX 3

The puzzle of progerias

Segmental progerias are genetic disorders in which individuals exhibit features of accelerated ageing. In humans, genetic defects that alter DNA repair and genomic integrity cause several progerias, including Werner syndrome and Hutchinson-Gilford syndrome¹⁰⁸. However, it remains actively debated as to what degree these diseases really are informative about normal ageing and whether the causative genes have any role in normal ageing. The fact that the cellular dysfunction seems similar to what occurs during normal ageing is certainly intriguing, but phenotypic similarity does not imply shared mechanisms. Among the progeroid models in which stem cell dysfunction has been studied are mice with defective DNA repair mechanisms and mice with defective telomere maintenance^{109,110}. HSCs derived from mice deficient in DNA double-strand break repair, nucleotide excision repair, or non-homologous end joining displayed hallmarks of premature ageing, including a decreased ability to give rise to committed progenitors with age¹¹¹. Stem cells in the seminiferous epithelium, skin and dentate gyrus of the hippocampus all show reduced size and cellularity as a consequence of reduced repair of DNA damage⁶. Mice defective in telomere maintenance clearly develop tissue defects, particularly in proliferative tissues that are highly stem cell dependent^{112,113}, and the phenotype as well as the shortened lifespan can be reversed by the expression of telomerase¹¹⁴. Together, these studies clearly demonstrate the importance of normal mechanisms ensuring genomic integrity for stem cell function. Nevertheless, whether changes in stem cell function are due to a disruption of these processes during normal ageing remains to be determined.

Changes in tumour suppressor responses downstream of DNA damage

The cellular response to DNA damage may likewise affect stem cell function. Telomere erosion and un-repaired DNA damage both trigger a p53-mediated cell cycle arrest or senescence⁹³. Mutant mice with hyperactive p53, despite exhibiting reduced rates of cancer, also develop progeroid syndromes^{94–96}. However, it is not known if p53 induction occurs during normal ageing of somatic stem cells, potentially leading to their senescence. As with the increases in p16/p19 noted above, this could conceivably be an adaptive mechanism to suppress proliferation in a cell population prone to malignant transformation. Nevertheless, mice with increased levels of p53 (subject to normal regulatory mechanisms) exhibit lower levels of tumour formation and reduced oxidative damage, suggesting that p53 activity can protect against some ageing-associated phenotypes⁹⁷. These contradictory data emphasize a potentially important connection between p53 activity, ageing and longevity. The protective role of tumour suppressors, such as p16 and p53, in limiting proliferation and triggering senescence is at odds with maintaining adequate levels of stem cell activity for tissue homeostasis and repair, but constitute possible examples of antagonistic pleiotropy (Box 1).

Future directions

This review presents an overview of the emerging picture of how stem cells age and the potential mechanisms underlying this process. Several trends can be identified. For example, in some tissues, stem cell numbers and activity decline with age, whereas in others, stem cell number seems to remain the same or even increase. However, in the latter examples, the differentiation potential of progenitors derived from aged stem cells is altered in such a way that tissue homeostasis is disrupted. Both intrinsic and extrinsic changes could contribute to aged stem cell phenotypes, including genetic and epigenetic changes that lead to altered gene expression profiles, as well as a decline in local and/or systemic factors that promote stem cell self-renewal and maintenance. Heterochronic studies have demonstrated that altering the systemic environment can influence age-related changes in tissue homeostasis, indicating that these changes in stem cell activity may be amenable to therapeutic intervention, once specific factors have been identified. Understanding the underlying mechanisms by which stem cells and their niches age will also improve our ability to recapitulate age-related disease models *in vitro*. As similar ageing stem cell phenotypes have been described in multiple model organisms, future studies should focus on identifying conserved pathways, such as the IIS pathway, that regulate stem cell dynamics and may coordinate cellular, tissue and organismal ageing.

Studies in model organisms such as *Drosophila* indicate that it may be possible to delay tissue ageing and increase lifespan by targeting stem cells and their daughters. They provide a platform to test whether delaying age-related changes to stem cells in one tissue provides protection against ageing in other tissues in a non-autonomous manner through systemic signals. If so, delaying stem cell ageing could improve the overall health of the organism and facilitate the development of specialized stem-cell-based therapies.

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Figure 1.

Emerging paradigms for stem cell ageing. **(a)** A generic model of normal stem cell function. A quiescent stem cell is activated, divides asymmetrically to give rise to a new stem cell (self-renewal) and another daughter that will undergo proliferative expansion and differentiation. **(b)** Paradigms of abnormal function of aged stem cells. **(A)** Failure of self-renewal. Both daughters differentiate, leading to a gradual depletion of the stem cell pool. **(B)** Impaired stem cell response can arise from a decline of extrinsic signals, a decline of stem cell responsiveness or both. **(C)** Aberrant differentiation. Multiple and different cases of this defect have been observed and two examples are illustrated. In one case, the normal distribution of progeny among potential fates is abnormally skewed towards one fate. In the other case, some daughters acquire abnormal fates that are not part of the normal repertoire. In the case of the *Drosophila* ISCs, as described in the text, this occurs without proceeding through a proliferative phase. **(d)** Senescence or apoptosis. Direct senescence and apoptosis of the quiescent stem cell are shown, but this could also occur among the progeny following activation.