5. Aging stem cells and their niches: possibilities for regenerative medicine

Amy J. Wagers

Aging is the single largest risk factor for many chronic diseases, and given the incredible gains in life expectancy witnessed throughout the globe over the past century, age-associated diseases now represent a rapidly growing, and largely unmet, medical need. It is clear from these trends that significant effort should be placed on the development of new medicines to treat age-related disorders, but how should we proceed? Will it be most effective to develop independent therapies specifically addressing each malady (e.g. separate treatments for heart failure, for muscle wasting, for osteoporosis)? Or, can we target the common denominator – aging itself, and the changes that occur in cells and tissues as a result of aging – to develop new platform interventions that take aim at the root causes of age-associated malfunctions? The answer to the strategic dilemma is still unclear, but accumulating evidence supporting critical systemic influences on aging and apparent "coordinating centers" of the ageing process, argue that a harmonized approach may indeed prove fruitful. This review discusses recent data, primarily in mammalian systems, that supports the hypothesis that central regulation of aging processes may be targetable for developing new therapies that could simultaneously impact the emergence and progression of multiple age-related disorders.

1 Aging and Stem Cells

In mammalian tissues, aging typically is accompanied by a progressive loss of homeostasis and impairment of regenerative potential. This association argues for a particular focus on changes that occur in the body's stem and progenitor cells with age because it is the primary role of these cells to maintain and regenerate tissue function throughout life.

[Keywords]
stem cells, stem cell niche, aging, regenerative biology, heterochronic parabiosis

1) Hematopoietic stem cells

Within adult tissues, stem cells have a unique plasticity that enables them to both self-renew and differ-

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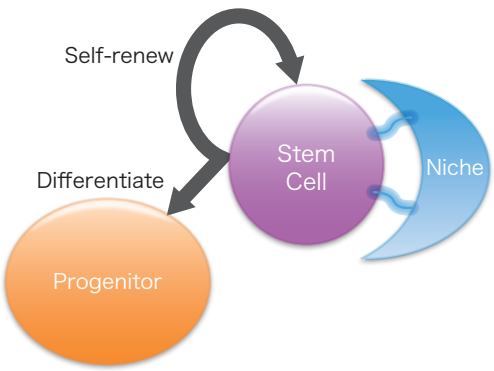

Figure 1
Stem cells are unique precursors capable of both self-renewal and differentiation to produce transit amplifying progenitor cells, which proliferate for a limited period of time before committing to terminal differentiation. Stem cell self-renewal and differentiation are regulated by signals from their niche, an anatomical microenvironment comprising stromal support cells, soluble factors, adhesion proteins and mechanophysical signals.

entiate to produce tissue-specific effector cells, which carry out primary organ functions (**Figure 1**). For example, the continuous production of mature blood cells in adult animals is assured by the presence of a rare population of multipotent hematopoietic stem cells (HSCs), which can be isolated from the bone marrow (BM). HSCs are defined functionally by their capacity to maintain production of all types of blood cells, including additional HSCs, for life or longer [1]. However, the efficiency of this hematopoietic activity declines with age, and aged HSCs exhibit impaired hematopoietic reconstitution capacity [2)-6)] as well as skewing of cell fate determination. The bias in hematopoietic differentiation that arises with age enhances myeloid cell production and impairs lymphoid cell production in both mice and humans [6) 7)], and has been proposed to underlie the predisposition to myeloid malignancies and deficiencies in acquired immunity that characterize old age [2)-4) 7)].

2) Skeletal muscle stem cells

Regenerative replacement of mature cells in skeletal muscle is similarly supported by a specialized population of skeletal muscle stem cells, also known as "satellite cells". These cells, which were originally defined anatomically [8)], are located immediately adjacent to and beneath the basal lamina of muscle fibers and respond to muscle damage by generating differentiated myoblasts that fuse form multinucleated myotubes (reviewed in Ref. 9, 10). As muscle ages, its regenerative activity declines, resulting in slow or incomplete recovery from injury and potentially contributing to age-associated muscle deterioration (sarcopenia). Impaired regeneration of muscle in older animals appears to be caused in part by acquired defects in satellite cell activation and proliferation, although alterations in the microenvironment of aged muscle also play a key role [11)-13)].

2 Regulation of stem cell function by the local and systemic microenvironment

1) Stem cell niches

As an organism ages, stem cells confront a variety of cellular challenges that perturb their self-renewal and differentiation capacity and ultimately lead to a breakdown of homeostasis and regeneration. These cellular assaults include accumulated DNA damage and telomere shortening, mitochondrial damage and metabolic reprogramming, and proteotoxicity [14)-17)]. Yet, not all age-associated declines in stem cell activity can be attributed to changes in the stem cell itself. Proper maintenance of stem cell function depends critically on anatomically defined elements, termed "niches", within tissues that comprise a complex network of support cells, growth factors, adhesion molecules and biophysical and mechanical signals that play a unique role in protecting and regulating stem cells and help to balance their self-renewal and differentiation activities

(Figure 1). For HSCs, several niches have been described in the bone marrow, and it is clear that vascular, osteogenic, neural and stromal cells each contribute importantly to stem cell regulation. For satellite cells, the differentiated muscle fiber itself seems to provide an essential niche for maintenance of muscle regenerative function, though signals from nearby stromal cells, inflammatory cells, blood vessels and motor neurons are also important. In addition to local contributors, stem cells throughout the body are also influenced by soluble factors provided via the circulatory system.

2) Aging of stem cell niches

Both the cellular and soluble components of the stem cell niche undergo significant changes with age. In both the bone marrow and skeletal muscle, aging is accompanied by an accumulation of adipocytes, which replace the hematopoietic and myogenic components of these tissues, respectively. Changes in the cellular composition of the niche can prevent the appropriate interaction of stem cells with their normal support cells, leading to dysregulation of regenerative function. In addition, age-associated alteration in non-cellular factors, including increased inflammatory cytokines and reactive oxygen species, may also negatively regulate the ability of a stem cell to properly differentiate or self-renew.

In summary, aging stem cells are subjected to a series of intrinsic and extrinsic changes that limit their ability to support proper tissue maintenance and regeneration. Thus, targeting the stem cell directly, or targeting its microenvironment, could provide therapeutic rejuvenation of tissue homeostasis and repair.

3 Evidence of conserved responses to "rejuvenating" interventions across tissues

Several recent studies, many focused on stem cells and their regenerative functions, have demonstrated that certain interventions can restore "youthful" function to multiple, distinct aged tissues. For example, studies in the skeletal muscle, liver, central nervous system and heart indicate that exposure to a young circulatory system is sufficient to reverse the degenerative decline of these tissues in aged mice [18)-22)]. The cellular and molecular mediators of these effects are just beginning to be uncovered (Figure 2), and thus far include inflammatory cells [20)], cytokines (CCL11 [21)]) and growth factors (Wnt [18)] and GDF11 [22)]), which may impact cell function in multiple aging tissues. Likewise, acute deletion of tissue-resident senescent cells has been shown to reverse age-related pathologies in the fat, skeletal muscle and eye in a mouse model of accelerated aging [23)], and telomerase re-activation in telomere-deficient animals was reported to improve neuronal phenotypes in these animals and dramatically alter neurological activity [24)]. Finally, calorie restriction (CR), probably the most broadly studied intervention that can prevent or reverse age-related pathologies, has been shown significantly reduce the incidence of a variety of diseases including cancer, diabetes, and atherosclerosis [25) 26)]. CR also extends lifespan in many organisms (though perhaps not primates [27) 28)]), and enhances stem cell function in multiple organs, including delaying the loss of hematopoietic repopulating ability of HSCs in aged mice [29)], reversing impairments in skeletal muscle regeneration through improved satellite cells function [30)], enhancing neurogenesis and cognitive function [31)], and accelerating intestinal regeneration by increasing the number of intestinal stem cells [32)]. The beneficial impact of CR appears to reflect both direct modification of tissue stem cells and modulation of stem cell niches. Thus, observations in many different experimental systems support the notion that common signals regulate the emergence and expression of aging phenotypes across tissues.

4 Aging "control centers"

As discussed above, aging induces functional decline in tissues throughout the body and common signals appear to rejuvenate multiple aged organs – do these observations reflect a broad and equivalent detrimental impact of aging on all tissues, or, do age-dependent changes in some organs actually initiate the process, eventually inducing such changes in others? The answer to this question is of critical importance to selecting a translational path for the treatment of age-related diseases. If aging affects tissues independently, then the mechanisms and impacts of this process must be determined for each cell type; however, if certain tissues play a coordinating or instigating role in aging, then research efforts focused more specifically on cells in these tissues, and the mechanisms by which they communicate aging signals with other cell types, may yield interventions that provide widespread benefits to aging organisms.

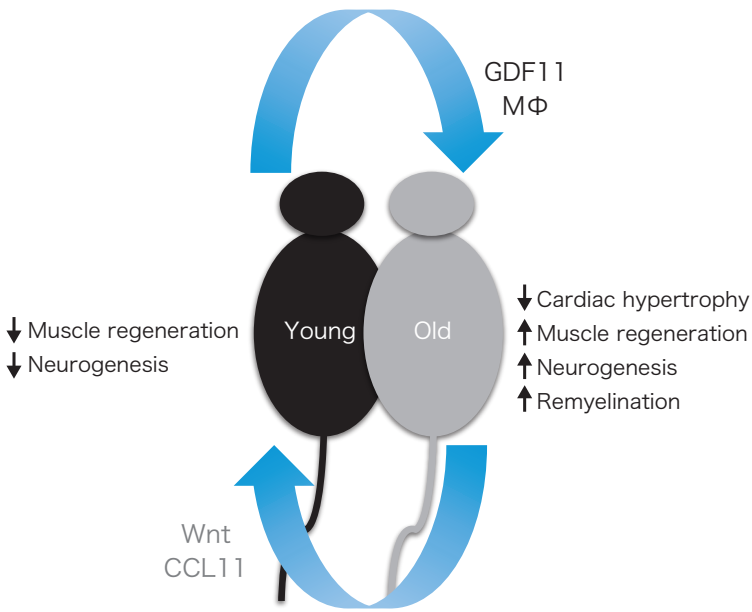

Figure 2
Heterochronic parabiosis studies in mice reveal the importance of blood circulating factors in phenotypes of aging. Soluble factors (GDF11) and cells (macrophages, MΦ) from the young partner rejuvenate the heart, skeletal muscle and nervous system of old partners, and soluble soluble factors (Wnt, CCL11) from the old partner suppress muscle regeneration and neurogenesis in young animals.

1) Evidence from invertebrate models

Some of the most compelling data in support of the existence of aging "control centers" comes from studies in invertebrate model systems. For example, in the nematode *C. elegans*, ablation of germline stem cells or reduction of insulin/insulin-like growth factor-1 signaling (IIS) in neurons or fat tissue extends lifespan and ameliorates age-related degeneration in other tissues [33)-39)]. Similarly, tissue-specific reduction of mitochondrial function in the intestine and nervous system at a specific stage in nematode development slows aging and extends lifespan through a cell non-autonomous mitochondrial stress response [40)], and enhancement of proteostasis specifically in the skeletal muscle of aging fruitflies reduces the accumulation of protein aggregates in other tissues, in part by altering feeding behavior and the release of insulin-like peptides (dilps) from median neurosecretory cells in the brain [41)].

2) Evidence from mammalian systems

The importance of inter-organ communication in the emergence and progression of age-related alterations in tissue function has also been supported by studies in mammalian systems. For example, fat-specific deletion of the insulin receptor in FIRKO mice promotes insulin sensitivity and resistance to obesity and significantly extends lifespan [42)]. Likewise, suppression of NF-κB signaling in the hypothalamus or brain of aging mice was shown recently to enhance muscle size and strength, dermal thickness, bone mass and cognition [31)]. The systemic effects of suppressing inflammatory signals in the neuroendocrine system were linked in this study to the secretion of gonadotropin-releasing hormone (GnRH), which appears to inhibit the emergence of aging characteristics in various tissues. Additional support for a hypothalamus-controlled systemic signaling system regulating functional deteriorations in aged mice comes from analysis of transgenic mice that overexpress the metabolic regulator SIRT1 in a brain-specific manner [43)]. These brain-specific SIRT1 overexpressing, or "BRASTO", mice exhibit extended lifespans, coupled with amelioration of age-related declines in several physiological parameters including physical activity,

body temperature, oxygen consumption and sleep quality. These beneficial effects of SIRT1 overexpression in the brain appear to relate to upregulation of orexin type 2 receptors (Ox2r) in a specific subset of neurons that shows increased activity in the hypothalamus of BRASTO mice [43], though precisely how these changes translate into improved function of peripheral tissues such as skeletal muscle and increased lifespan remains to be determined. Taken together, these and other studies support the notion that age-related phenotypes are strongly regulated by the endocrine (and particularly neuroendocrine) system. Moreover, they argue that certain tissues play a predominant role in setting the pace of aging for the entire organism and point to the importance of tissue crosstalk and long-range signaling in the determination of lifespan and the emergence of aging pathologies in both invertebrate and mammalian systems.

5 Conclusions and perspective

Significant evidence now exists to indicate that the process of aging involves complex interactions among diverse organ systems, with certain tissues – such as the innate immune and nervous systems – playing particularly critical roles in regulating the emergence and progression of age-related phenotypes. This integration of aging physiology appears to depend also on a conserved system of systemically-regulated signaling pathways and age-dependent alterations in critical circulating factors that can evoke the functional deterioration of aged cells. From these data, it is reasonable to propose therapeutic strategies that target the central regulators of the aging process to promote more youthful function broadly across tissues (**Figure 3**). Such interventions hold significant promise for closing the gap between healthspan and lifespan and promoting tissue maintenance and regeneration throughout life. Enhancement of stem cell function in aged tissues will be key in achieving these goals, and likely will require a two-pronged attack to prevent or revert intrinsic alterations in stem cells that impair their function and to protect or restore the stem cell microenvironment to optimally support the activity of these cells. Recent years have witnessed many exciting discoveries that have brought us much closer to understanding the mechanistic basis of aging and its associated pathologies and these advances should accelerate development of new clinical approaches to ameliorate age-related disease.

Figure 3
Aging is the single most significant risk factor for many degenerative diseases. Can therapies for these diseases target the "root cause" – common mechanisms regulating the aging process – to develop common interventions for age-associated diseases?

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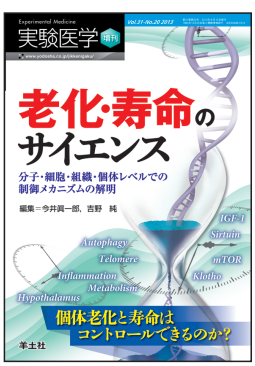

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