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Regulation of Senescence in Cancer and Aging

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1. Introduction

Senescence was first described as a state of irreversible growth arrest that normal human fibroblasts enter at the end of their replicative lifespan [1]. This phenomenon has been observed in a variety of somatic cells derived from many species, which is in contrast to the infinite replicative capacity displayed by germline, cancer, and certain stem cells [2]. Senescent cells are irreversibly arrested in G1/G0 phase of the cell cycle and lose the ability to respond to growth factors [3, 4]. They show sustained metabolic activity for long periods of time [5] and become resistant to apoptosis [6, 7]. In addition, senescent cells undergo distinctive changes in morphology to a flat and enlarged cell shape [8] and are often accompanied by the induction of acidic senescence-associated β-galactosidase (SA-β-gal) activity [9]. At the molecular level, alterations in gene expression specific to senescent cells have been identified [10–14], including those constituting senescence-associated secretome, which can trigger profound changes in the surrounding cells and microenvironment [15–17]. The changes of gene expression in senescent cells can be partially explained by alterations in chromatin structure [13], including the formation of senescence-associated heterochromatic foci (SAHF), which is associated with trimethylated lysine 9 of histone H3, heterochromatin protein 1, and high-mobility group A protein [18–20]. The formation of SAHF requires the recruitment of pRb to E2F-responsive promoters and is responsible for the stable repression of E2F target genes, possibly contributing to the irreversibility of senescence [18].

2. Telomere-Dependent Replicative Senescence and Telomere-Independent Premature Senescence

The onset of replicative senescence is determined by the number of times that a population of cells can divide, suggesting that a mitotic clock recording cell divisions governs this cellular process [21, 22]. The discovery that telomeres get progressively shortened with each cell division provides a plausible explanation for the nature of this mitotic clock [23–26]. Because of the inability of DNA polymerases to replicate DNA at the very ends of linear chromosomes, telomeres become progressively shortened during successive cell divisions [23, 27, 28]. Telomerase, which is responsible for de novo synthesis of telomeric repeats and maintenance of telomere length [29], is expressed in germline, stem and cancer cells, but undetectable in majority of normal somatic cells [30, 31]. In the absence of telomerase, progressive telomere shortening is thought to be the major cause of replicative senescence. Supporting this notion, enforced expression of the telomerase catalytic subunit (TERT) has been shown to prevent telomere shortening and extend
the lifespan of human somatic cells [32–34]. Conversely, inhibition of telomerase in immortal cells has been found to limit their replicative lifespan [35, 36]. Critically shortened telomeres lose the protection of telomere-binding proteins, leading to telomere “uncapping” [26]. Recent studies have revealed that DNA damage foci containing multiple DNA damage-response proteins, such as 53BP1, γH2AX, MDC1 and MRE11, are found at telomeres in senescent cells, suggesting that uncapped telomeres are recognized as DNA breaks and thus trigger a DNA damage response [37–39].

In addition to telomere attrition, senescence can be activated by many types of stress, including aberrant activation of certain oncogenes [40–42], damage to chromatin structure [43–45], oxidative stress [46–48], DNA damage [49, 50], and inadequate culture conditions [48, 51, 52]. Collectively, they are referred to as stress-induced premature senescence. Among these senescence-inducing stimuli, oxidative stress has been shown to accelerate telomere shortening [47, 53], possibly by inducing telomeric single-strand breaks [54]. However, stress-induced premature senescence, unlike replicative senescence, is largely independent of the telomere length or the number of cell divisions [55–57]. The final outcome of both replicative senescence and stress-induced premature senescence is remarkably similar in that they share common changes in cell cycle regulation and morphological properties [40, 41, 46, 49, 50, 58, 59]. Although gene expression pattern can vary depending on the specific types of tissues and cells or the specific stimuli to trigger the senescence response, senescent cells display a unique pattern of gene expression that differs from proliferating cells or quiescent cells. In addition to the cell cycle regulatory genes, the expression of DNA damage checkpoint genes, inflammation and stress-associated genes, genes encoding extracellular matrix proteins and extracellular matrix-degrading enzymes, and cytoskeletal genes and metabolic genes is generally altered during replicative and premature senescence. Recent studies suggest that DNA damage could be a common cause for different forms of senescence induced by various stimuli [11, 12, 14, 60–63]. Senescence is now considered as a general stress response in normal cells to various types of cellular damage [64].

3. Molecular Regulation of Senescence

Despite the commonality shared by senescence induced by various stimuli, regulation of senescence varies significantly among cells derived from different species, or even different types of cells from the same species [65]. For example, telomere shortening is the major cause of senescence in human fibroblasts [34], whereas mouse fibroblasts undergo senescence that is independent of telomere shortening and probably mediated by oxidative stress [48, 52]. Diverse senescence-inducing stimuli can trigger the senescence response through multiple genetic pathways. However, these pathways seem to converge on p53 and pRb, and inactivation of both the p53 and pRb pathways is often required to prevent the activation of senescence [66–70].

In senescent cells, p53 is phosphorylated and its transactivation activity is elevated, although its mRNA and protein levels are largely unchanged [38, 71–74]. DNA damage response elicited by telomere dysfunction leads to activation of ATM/ATR and Chk1/Chk2, which in turn phosphorylate and stabilize p53 [37–39, 75, 76]. In addition, p53 is activated and plays an important role in stress-induced premature senescence [40, 50, 77–79]. This p53 activation is mediated by p14ARF (or p19ARF in mouse) encoded by the INK4a/Arf locus. ARF stabilizes p53 by sequestering Mdm2, an E3 ubiquitin ligase targeting p53 for degradation [80]. The ARF-p53 axis plays an important role during senescence in mouse cells. Inactivation of p53 or ARF in mouse embryo fibroblasts (MEFs) is sufficient to prevent senescence [81–83].

One of the p53 targets is p21(CIP1/WAF1) (p21), whose increased expression transactivated by p53 is responsible for cell cycle arrest [84]. The expression of p21 is up-regulated during replicative senescence [85–89]. This p21 up-regulation is dependent on signal(s) initiated by telomere shortening, as expression of TERT blocks this up-regulation [89–91]. Overexpression of p21 is able to induce a senescence-like growth arrest in some cells [92, 93], while deletion of p21 can postpone senescent arrest [94, 95]. Collectively, these studies suggest that p53 regulates senescence at least in part by inducing p21. As a cyclin-dependent kinase inhibitor, up-regulation of p21 in senescent cells leads to inhibition of pRb phosphorylation, which controls cell cycle progression [18, 84]. There are instances that inactivation of either p53 or pRb can significantly delay the onset of senescence, supporting a linear p53-pRb pathway [68, 96]. In many other instances, both p53 and pRb need to be inhibited to prevent replicative senescence, suggesting two independent pathways [66–69].

In parallel to p21, p16INK4a (p16) is another cyclin-dependent kinase inhibitor that leads to pRb hypophosphorylation [84]. The expression of p16 is increased during replicative senescence [88, 97–99], but whether increased p16 expression is regulated by telomere shortening is controversial. As telomere shortening is the major cause of replicative senescence in human fibroblasts [34], and inactivation of both the p53 and pRb pathways is required to prevent replicative senescence [67], it is reasonable to expect that dysfunctional telomeres may signal into p16-pRb axis. There is indeed an example showing that telomere dysfunction induces p16 expression [69]. However, the dynamics of p16 and p21 elevation in senescent cells are different. The increased expression of p16 occurs after senescence has already been established in culture [88, 97, 98, 100], in contrast to the rapid increase of p21 expression in cells approaching replicative senescence [89]. Within a senescent population of human cells, some cells express p16, while others express p21 [38, 96, 100]. DNA damage foci at telomeres are found only in cells expressing p21, but not in p16 positive cells [38], suggesting that p16 elevation is independent of telomere shortening. Consistent with this notion, p16 induction during senescence, unlike p21, is not prevented by ectopic expression of TERT [53].
The expression of p16 is readily increased during premature senescence induced by a variety of stress [40–42, 49, 51, 101]. It is not entirely clear how p16 expression is regulated by various senescence signals [102–104]. Under certain circumstances, p16 is coordinately regulated with Arf, which is also encoded by the INK4a/Arf locus. For example, polycomb complex proteins have been shown to repress the INK4a/Arf locus [100, 105–108]. Decreased expression of polycomb complex proteins relieves the repression of the INK4a/Arf locus and is responsible, at least in part, for the elevation of p16 and Arf in senescent cells [100, 106, 107]. The expression of p16 and Arf can also be regulated independently. Id1, whose expression is decreased in senescent cells [109], has been shown to specifically suppress p16 expression by forming heterodimers with transcriptional factors Ets1/2 or E47 and inhibiting their ability to transactivate p16 [110–112]. Down-regulation of Id1 in human and mouse fibroblasts has been shown to induce p16 expression and senescence [110, 112], while ectopic expression of Id1 delays senescence in human fibroblasts, mammary epithelial cells, keratinocytes, and endothelial cells [98, 113–115], suggesting an important role for Id1 in regulating p16 and senescence.

The expression of p16 varies significantly among different human cell lines [100], and this variable expression seems to hold the key to as whether p53 and pRb function in a linear manner or in parallel. In cells with low or no p16 expression, p53 and pRb may function in a linear pathway, whereas p53 and pRb work in parallel in cells with significant p16 expression. In mouse embryo fibroblasts (MEFs), inactivation of p53 or ARF, but not p16, is sufficient to prevent senescence [81–83, 116], indicating that p53-Arf axis is the major regulator of senescence pathway in mouse cells. Human mammary epithelial cells quickly encounter a growth arrest state that is not associated with telomere shortening but mediated by p16 up-regulation [33, 101]. A subset of cells with p16 inactivation emerge from the arrest population and continue to divide until reaching a second growth arrest state that is associated with telomere shortening [33, 51, 101]. Depending on cell types, culture conditions, and the extent of stress, inactivation of either p53-p21-pRb or p16-pRb pathway individually, or both pathways together, is required to prevent senescence.

4. Senescence As a Barrier to Tumorigenesis

Tumorigenesis is a multistep process, in which a normal cell acquires mutations in a number of cancer-causing genes [117]. By restricting cell proliferation and thereby impeding the accumulation of mutations, senescence acts as an important tumor suppression mechanism. Furthermore, senescence induced by aberrant activation of oncogenes, oxidative stress, or DNA damage prevents cells at risk of malignant transformation from proliferating [55, 59, 118, 119]. Senescence represents a physiologic response that cells must overcome in order to divide indefinitely and develop into tumors. Consistent with the notion that senescence is a tumor suppression mechanism, well-established tumor suppressors, including p53, pRb, p16, Arf, and p21, are regulators of senescence [102, 118, 120].

In contrast to normal somatic cells, cells derived from tumors divide indefinitely in culture. The ability to escape senescence (i.e., immortality) is a necessary step for cells to become transformed and one of the hallmarks of cancer cells [120]. 80%–90% of human cancer cells acquire unlimited proliferative potential through reactivation of telomerase [30, 31], while the rest maintain telomere length by a recombination-mediated process termed alternative lengthening of telomeres [121, 122]. These observations in human cancer strongly suggest a connection between telomere checkpoint and tumor suppression. Supporting this connection, inhibition of telomerase activity in cancer cells limits their growth by triggering telomere shortening and cell death [35, 36]. Conversely, ectopic expression of telomerase in normal human cells leads to immortalization and enhances the ability of these cells to be neoplastically transformed [33, 34, 123]. Furthermore, transgenic mice overexpressing TERT show increased propensity to tumorigenesis [124–128].

Genetic studies in mice deficient in telomerase provide further support for telomere shortening as a tumor suppression mechanism. Mice deficient in the telomerase RNA component (mTERT−/−) gradually lose telomeres over several generations [129], and tumorigenesis is significantly reduced in late generations of mTERT−/− mice with telomere attrition [130–140]. Decreased tumorigenesis is also observed in late generation of mice with a null mutation in telomere catalytic subunit (mTERC−/−), and p53 mutation enables tumor progression in these mice [141]. More importantly, two recent studies provide evidence that senescence induced by telomere shortening is responsible for tumor suppression [142, 143]. When apoptosis is blocked by the expression of Bcl-2 or a specific p53 mutant (R172P), shortened telomeres reduce tumorigenesis in mTERC−/− mice. Suppression of tumor development requires p53-dependent activation of senescence [142, 143], demonstrating that senescence induced by telomere shortening is an effective tumor suppression mechanism in vivo.

The discovery that oncogenic Ras protein can induce a senescent arrest after causing an initial hyperproliferation in normal cells suggests that induction of senescence is an intrinsic cellular response that prevents cells at risk from proliferating [40]. In mouse tumor models with oncogenic Ras, senescent cells are found in premalignant lesions in lung [61], spleen [144], breast [145], and pancreas [146]. The observation of senescent cells has been extended to many premalignant lesions or benign tissues induced by different oncogene activation or tumor suppressor inactivation in mouse [147–155] and human [148, 156–159]. Importantly, senescent cells are absent in malignant tumors [61, 144, 145, 147–150, 152, 156, 158, 160], suggesting that oncogene-induced senescence is a powerful tumor suppression mechanism by restricting proliferation of cells with oncogenic mutations and this senescence block must be evaded for malignancy to progress. Consistently, deletion of senescence regulators such as p53, Arf, p16, p27, SUV39H1 or PRAK abrogates senescence and causes progression of tumors to
the malignant stage [144–146, 148–150, 152, 153, 160]. These observations point to a causal link between loss of senescence and malignant transformation.

5. Senescence in Anticancer Therapy

In theory, senescence offers an attractive therapeutic option if it can be induced in tumor cells. Because of the uncertainty in reactivating in cells, a response that otherwise has been overcome, senescence remains as an underappreciated therapeutic approach [161, 162]. Surprisingly, many cancer cells retain the ability to senesce either spontaneously or in response to external stress stimuli, even though most cancer cells have overcome the senescent arrest during tumorigenesis. As tumors often develop resistance to apoptosis induced by anticancer treatment, induction of senescence in tumor cells serves as an alternative approach in cancer therapy, and could be especially effective in treatment of cancer cells in which apoptotic pathways are disabled [163].

Telomerase is an attractive target for inducing senescence in cancer cells. As telomerase is critical for the maintenance of telomere length [29], inhibition of telomerase in cancer cells leads to shortening of telomeres, which is a major cause of senescence activation [24, 33, 34]. Since 80–90% of human cancers acquire unlimited proliferative potential through activation of telomerase [30, 31], the strategy of inhibiting telomerase in cancer therapeutics targets a broad range of malignancies. In addition, this approach offers desired specificity in targeting cancer cells, as telomerase is expressed in most cancer cells, but undetectable in the majority of normal cells including adult stem cells [164, 165]. The emerging cancer therapeutics targeting telomerase include small molecule or oligonucleotide inhibitors of telomerase enzymatic activity, antitelomerase immunotherapy, inhibitors of telomerase expression and telomere-disrupting agents [166–168]. The strengths and weaknesses of these different approaches are discussed in an excellent review [166]. Although apoptosis is induced by inhibition of telomerase in some studies, induction of senescence as a result of telomerase inhibition is clearly demonstrated to be responsible for tumor suppression [169–173]. The effectiveness of these approaches has been demonstrated in many studies [174–177], and several clinical trials targeting telomerase for cancer therapeutics are now ongoing [166].

Senescence induced by oncogene activation or inactivation of tumor suppressor genes must be evaded for tumors to progress to full malignancy, which is often associated with inhibition of crucial senescence regulators. Reactivation of senescence response offers a great opportunity in cancer therapeutics. Considering the critical role of p53 in senescence regulation and common occurrence of p53 mutations in cancer cells, p53 is an attractive target for reactivation of senescence in cancer cells. Various approaches have been developed to target p53 in order to restore normal p53 function in cancer cells, including pharmacological depletion of mutant p53 protein [178, 179], restoring normal function in mutant p53 [180, 181], and reactivation of p53 [182–189]. In most of these reports, apoptosis is the overwhelming response that is responsible for tumor suppression. Senescence as a tumor suppression mechanism after restoring p53 expression has been demonstrated in two recent elegant studies [190, 191]. In a mouse model of hepatocellular carcinoma, reactivation of p53 in these tumors results in rapid activation of senescence and subsequent immune cell infiltration which leads to clearance of tumor cells [191]. In a separate study, restoration of p53 in p53-deficient mouse models of lymphoma, and osteosarcoma leads to tumor regression. Apoptosis is selectively induced by p53 in lymphomas, while senescence induced by p53 in osteosarcomas is responsible for tumor regression [190], suggesting that tissue type and/or genetic context play a critical role in determining the cellular response in p53-mediated tumor regression. Taken together, restoration of p53 function in tumors offers an effective way to restrict tumor growth by inducing senescence or apoptosis. As p16 and p21 have been shown to induce senescence efficiently [92], these senescence regulators together with Arf and pRb may provide additional targets for the effective activation of senescence in cancer therapeutics.

In addition to restoration of tumor suppressor genes, oncogene inactivation offers another possible intervention to induce senescence in cancer cells. Suppression of c-Myc oncogene induces senescence and leads to tumor regression in diverse tumor types including hepatocellular carcinoma, lymphoma and osteosarcoma [192]. Senescence induced by Myc inhibition depends on critical senescence regulators such as p53, p16 or pRb. Inactivation of these senescence regulators impairs senescence induction and tumor regression [192]. Inhibition of Myc as therapeutic intervention is further illustrated in lung carcinoma mouse model initiated by oncogenic Ras. Inhibition of Myc triggers rapid tumor regression associated with apoptosis and senescence induction [193]. These studies indicate that senescence response not only is functional in cancer cells, but also can be reactivated to cause tumor regression. Furthermore, these studies suggest that therapeutic intervention aimed at molecules required to support tumor growth may also lead to senescence induction and ultimately tumor regression.

The finding that senescence can be induced by DNA damage [49, 50] suggests that chemotherapeutic drugs, which cause DNA damage, may activate senescence in tumor cells and therefore determine the drug response in cancer treatment [194]. Chemotherapeutic drugs induce senescence in various types of tumor cells in culture [195–199]. In a Myc-driven mouse lymphoma model, chemotherapeutic drug cyclophosphamide induces p53- and p16-dependent senescence in lymphomas, leading to better prognosis following chemotherapy [163]. In human breast cancer, a high percentage of tumors after chemotherapy show positive staining for senescence markers, and induction of senescence in these tumors is associated with p53 and p16. Induction of senescence is not observed in tumors before chemotherapy [199], suggesting that senescence observed in tumors is induced by chemotherapy. Taken together, these studies show that senescence induction can positively influence the outcome of cancer treatment. Senescence-inducing drugs may be effective
alone or in combination with classic therapeutic approaches to reduce tumor growth and toxicity to normal cells.

6. Senescence and Aging

Aging is characterized by progressive deterioration of physiological function in all tissues and organs after a period of development. This biological process is associated with increased susceptibility to major chronic diseases and ultimately mortality. Since the discovery of senescence in cultured cells, it is recognized that cellular senescence and organismal aging may be closely related because of their shared ability to limit lifespan [21]. It is hypothesized that constant tissue regeneration results in accumulation of senescent cells in somatic tissues, which limits tissue renewal, perturbs normal tissue homeostasis and ultimately leads to aging [59, 118, 200]. Cells with characteristics of senescence have been reported to increase with advancing age in mice, primates and humans [9, 201–206]. In addition, accumulation of senescent cells is linked with age-associated pathological conditions, such as osteoarthritis [207], atherosclerosis [208–211], dementia [212], liver cirrhosis [203], and respiratory disease [213, 214]. The initial support for the senescence theory of aging comes from the observation of an inverse correlation between the in vitro lifespan of cells and the age of donors from which they are derived [215–219], although this correlation has been disputed [220]. Subsequent support comes from studies of cells derived from progeroid patients, such as Werner syndrome, which achieve fewer cell divisions before entering senescence than cells derived from normal individuals of same age [221]. Direct evidence supporting senescence as one of the aging mechanisms, however, is still missing. It remains to be determined whether accumulation of senescent cells is responsible for aging or age-related diseases.

Recent studies suggest that telomere checkpoint plays an important role in the aging process. It is evident that telomere shortening occurs in aged human tissues [222–235], at sites of age-related pathological conditions [203, 236–243], or associated with stress and obesity [244, 245]. Although it remains to be demonstrated whether telomere shortening leads to the accumulation of senescent cells in vivo, and more importantly makes a substantial contribution to aging, studies of human premature aging syndromes support a link between telomere attrition and aging. Patients of dyskeratosis congenita and aplastic anemia have mutations in telomerase RNA or catalytic subunit [246–248], and are characterized by accelerated telomere shortening [239, 246]. Further evidence for a role of telomere attrition in aging comes from genetic studies of mice deficient in telomerase. While mice with a null mutation in telomerase RNA (mTERC−/−) are apparently normal in early generations, these mice in later generations gradually lose telomeres [129] and show accelerated aging phenotypes [140, 249]. Similarly, premature aging phenotypes are observed in mTERC−/− mice on a CAST/EiJ background, which have shorter and more homogenous telomere length than C576BL/6, strain. Even with the presence of telomerase, shortened telomeres in mTERC−/− mice on CAST/EiJ background are associated with premature aging [250]. A recent study shows that telomerase reactivation can reverse much of the premature aging phenotypes in telomerase-deficient mice [251], indicating that telomere attrition plays a critical role in aging. Furthermore, mutations in WRN or BLM in the telomere dysfunctional background in mouse cause premature aging phenotypes that are characteristics of Werner or Bloom syndrome in human. Such premature aging phenotypes are absent in mice with WRN or BLM mutation but with long telomeres [252, 253]. These studies clearly establish a link between telomere attrition and aging. Whether this link is mediated through senescence triggered by telomere shortening is currently unknown.

Premature aging phenotypes in late generation mTERC−/− mice are associated with reduced renewal capacity in highly regenerative tissues such as skin, intestine, bone marrow and reproductive organs [140, 249–251], suggesting that stem cells may be affected by telomere shortening. Tissue-specific or adult stem cells, which are capable of self-renewal and differentiation, are essential for the normal homeostatic maintenance and regenerative repair of tissues throughout the lifetime of an organism. The self-renewal ability of stem cells is known to decline with advancing age, eventually leading to the accumulation of unrepaired, damaged tissues in old organisms [59, 254–256]. By limiting cell proliferation, senescence in stem cells is hypothesized to contribute to aging by reducing the renewal capacity of these cells [21, 59, 118]. Not all stem cells express high level of telomerase. For example, human mesenchymal stem cells have no detectable telomerase activity [257], and hematopoietic stem cells from human and mouse have low level of telomerase activity [258–260]. Telomere attrition has been observed in these stem cells [257, 260–263]. It is possible that senescence induced by telomere attrition may occur in stem cells over the lifespan of an organism and would result in the reduction of the renewal capacity of stem cells. However, it remains to be determined whether stem cells undergo senescence during aging.

Several senescence regulators have been found to play a critical role in aging. The expression of p16 increases with advancing age in humans and rodents [264–270]. Increase of p16 in aged rodents is attenuated in several tissues (adrenal, heart, kidney, ovary, and testis) by caloric restriction [264], which potently slows aging. Moreover, age-related increase of p16 is found to be associated with a decline in the renewal capacity of stem cells in brain, pancreas, and hematopoietic system, and these stem cells derived from aged mice lacking p16 have increased regenerative potential [271–273]. In addition, p53 and p21 have also been implicated to impact aging. It has been shown that p21 is required to maintain quiescence of hematopoietic stem cells (HSCs). In the absence of p21, increased cell cycling leads to stem cell exhaustion, which is responsible for impaired self-renewal of HSCs [274]. Interestingly, deletion of p21 in late generation mTERC−/− mice improves stem cells function and rescues much of the premature aging phenotypes associated with telomere attrition [275]. HSCs from p53-deficient mice have increased stem cell population and enhanced renewal capacity [276, 277]. Suppression of
stem cells function by p53 is also observed in neural stem cells [278]. Furthermore, mice with excessive p53 activity maintain cancer protection, but age prematurely including impairment of HSCs [279–282], which is at least in part due to increased sensitivity to senescence-inducing stimuli [280]. Interestingly, concomitant increase of normal p53 and p19arf leads to increased longevity in mice [283], although elevation of p53 alone is not sufficient to increase longevity [284, 285]. Collectively, these recent studies support an emerging link between senescence regulation and aging, and show the potential importance of senescence regulation in stem cells aging.

Senescence is regarded as an antagonistic pleiotropy: beneficial as a tumor suppressor, but detrimental to organisms by contributing to aging. Great progress has been made in our understanding of senescence regulation in cancer and aging. Challenges remain as how to effectively utilize senescence as a potent treatment for cancer. The exact function of senescence-associated secretome in cancer and aging is of great interest and needs to be investigated. Investigation of telomere shortening and senescence in stem cells during physiological aging is much needed for our understanding of the role of senescence in aging, which leads to the intriguing question as whether inhibition of senescence may slow aging.

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