Published in final edited form as:
Semin Cancer Biol. 2011 December ; 21(6): 354–359. doi:10.1016/j.semcancer.2011.09.001.

Cellular senescence: a link between cancer and age-related degenerative disease?

Judith Campisi[a,b,*], **Julie Andersen**[a], **Pankaj Kapahi**[a], and **Simon Melov**[a]

Judith Campisi: jcampisi@buckinstitute.org; Julie Andersen: jandersen@buckinstitute.org; Pankaj Kapahi: pkapahi@buckinstitute.org; Simon Melov: smelov@buckinstitute.org

[a]Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato CA 94545 USA

[b]Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley CA 94720 USA

Abstract

Cellular senescence is an established cellular stress response that acts primarily to prevent the proliferation of cells that experience potentially oncogenic stress. In recent years, it has become increasingly apparent that the senescence response is a complex phenotype, which has a variety of cell non-autonomous effects. The senescence-associated secretory phenotype, or SASP, entails the secretion of numerous cytokines, growth factors and proteases. The SASP can have beneficial or detrimental effects, depending on the physiological context. One recently described beneficial effect is to aid tissue repair. Among the detrimental effects, the SASP can disrupt normal tissue structures and function, and, ironically, can promote malignant phenotypes in nearby cells. These detrimental effects in many ways recapitulate the degenerative and hyperplastic pathologies that develop during aging. Because the SASP is largely a response to genomic or epigenomic damage, we suggest it may be a model for a cellular damage response that can propagate damage signals both within and among tissues. We propose that both the degenerative and hyperplastic diseases of aging may be fueled by such damage signals.

1. Aging and age-related disease

Aging is the largest risk factor for developing a panoply of diseases, ranging from cancer to neurodegeneration. These age-related pathologies are generally chronic, and therefore cause lengthy periods of serious morbidity, and, for many, eventual mortality [1]. Do most of the diseases and chronic pathologies of aging arise independently? Or are these diseases linked by a common biology?

There is a growing consensus that the latter possibility may indeed be the case. In the last two decades, evolutionarily conserved signaling pathways have been identified that, when modified, can significantly extend life span and delay the onset of multiple aging phenotypes [2]. Thus, it now seems likely that one or more basic aging process underlies most, if not all, age-related pathologies. There are, however, a number of ideas, which are not necessarily mutually exclusive regarding the nature of these basic aging processes, and a number of mechanisms by which these processes are proposed to drive age-related disease.

[*]Corresponding author at: Buck Institute for Research on Aging, 8001 Redwood Boulevard, Novato, CA 94545 USA. Telephone: 1-415-209-2066 or 1-415-209-2043; Fax:1-415-493-3640.

Here, we discuss our recent progress in identifying one such basic aging process, and our hypothesis regarding potential mechanisms by which it might drive multiple age-related pathologies. Our hypothesis stems from studying one of the most prevalent of the age-related diseases: cancer.

2. Cancer and the degenerative diseases of aging

To begin to understand how multiple diseases of aging might be linked, we have found it is useful to consider age-related diseases as falling into one of two broad categories (Fig. 1). The first category we consider to be loss-of-function diseases. These diseases are by nature primarily degenerative. That is, they are caused by a loss of cells, subcellular function, tissue elements, or optimal cellular or tissue function. Examples of pathologies in this category include many of the neurodegenerative diseases and several aspects of cardiovascular disease, as well as pathologies such as macular degeneration, osteoporosis and sarcopenia, among others. The second category we consider to be gain-of-function diseases. These pathologies are generally hyperplastic in nature. As such, they are caused by a gain of cells and, in some cases, the acquisition of new cellular functions. Examples of pathologies in this category include benign prostatic and other hyperplasias and a component of atherosclerosis (arterial thickening due to smooth muscle cell proliferation). The most prominent and deadly of the gain-of-function diseases is, of course, cancer.

In classifying age-related diseases into these two categories, we can now ask a somewhat simpler question: is there a common biology that links cancer to the degenerative diseases of aging (Fig. 1)?

3. What causes cancer?

Decades of cancer research have illuminated much about the important risk factors for developing cancer, and so we now understand many of the genetic and environmental influences that significantly increase an individual's risk for developing a malignant tumor. However, indisputably, the most significant risk factor for developing cancer is advancing age. In humans, cancer incidence rises with approximately exponential kinetics after about 50 years of age [3, 4]. Thus, the vast majority of malignant tumors that are treated in clinics throughout the industrialized world occur in older patients [5].

Decades of cancer research have also identified two critical factors that are important for malignant tumorigenesis.

The first factor is internal to the cancer cell -- the accumulation of somatic mutations [6]. Cancer cells typically harbor many dozens of genomic alterations [7], the acquisition of which is often accelerated by early mutations that inactivate genes that are critical for maintaining genomic stability [8]. These oncogenic mutations provide cancer cells with strong selective advantages *in vivo*, and confer on them several functionally important malignant phenotypes. These phenotypes include unchecked cell proliferation, survival, motility and invasiveness, as well as the abilities to adapt to and proliferate in an ectopic environment, evade killing by the immune system, and alter the tissue microenvironment such that it supports the survival and growth of the tumor [9].

A second crucial factor for malignant tumorigenesis is external to the cancer cell -- a permissive tissue milieu [10–12]. Normal tissue microenvironments can suppress the ability of mutant cancer cells to proliferate and survive; this is why tumor cells often must acquire the ability to modify the tissue microenvironment [13, 14]. However, tissue microenvironments can also acquire a pro-carcinogenic state independent of the presence of tumor cells. One variable that promotes a pro-carcinogenic tissue milieu is age [15, 16]. The

mechanisms by which aging promotes a permissive tissue environment are incompletely understood and undoubtedly multi-factorial. Here, we discuss one such factor, cellular senescence, its role as a cellular response to stress and damage, and its known and hypothesized relationships to cancer and degenerative pathologies of aging.

4. Cellular senescence suppresses cancer

Cellular senescence generally refers to the essentially irreversible loss of proliferative ability that occurs when cells experience potentially oncogenic stimuli. The senescence response is now recognized as a potent and highly efficacious cell autonomous tumor suppressive mechanism [17, 18]. That is, damage or stress, which puts proliferative cells at risk for undergoing malignant transformation, induce cellular senescence in order to prevent the at-risk cells from initiating tumorigenesis. Consistent with this knowledge, the senescence growth arrest depends critically on the functions of the p53 and p16INK4a/pRB pathways [19, 20], which are, arguably, the two most powerful tumor suppressor pathways encoded by vertebrate genomes. Therefore, malignant tumorigenesis requires the genetic (mutational) or epigenetic inactivation of at least one, often both, of these tumor suppressor pathways, thereby enabling incipient cancer cells to bypass the senescence checkpoint.

The p53 and p16INK4a/pRB pathways establish and maintain the senescence growth arrest in response to myriad senescence-inducing stimuli. These stimuli include dysfunctional telomeres, non-telomeric DNA damage, disruptions to chromatin organization, the expression of certain activated oncogenes, strong or persistent mitogenic signals, and several types of cellular stress, including oxidative stress [21–25]. Not surprisingly, all of these senescence-inducing stimuli are potentially oncogenic. Germane to our central hypothesis, many of these stimuli directly or indirectly cause genomic or epigenomic damage. Also of interest, as discussed below, senescent cells have been shown to increase with age in a variety of mammalian tissues

5. The senescence-associated secretory phenotype (SASP)

The senescence growth arrest is not simply a halt to cell proliferation, akin to the reversible growth arrest of quiescence. Rather, senescent cells show marked and distinct changes in their pattern of gene expression. Thus, senescent cells enter a unique state – one that is distinct from quiescence or terminal differentiation [26]. Among the prominent senescence-associated changes in gene expression, there is a robust increase in the mRNA levels and secretion of numerous cytokines, chemokines, growth factors and proteases [27–32]. We term this phenotype the senescence-associated secretory phenotype (SASP).

Important features of the SASP include the fact that it is conserved between human and mouse cells [33], occurs in a variety of proliferative cell types (fibroblasts, epithelial cells, endothelial cells, astrocytes, etc) [29, 34, 35], and occurs *in vivo* in both mice and humans [27, 29, 31, 32]. The SASP is initiated in large measure by the transcriptional induction of the plasma membrane-bound form of the cytokine IL-1α, and its subsequent juxtacrine signaling within the membrane through its receptor [36]. Subsequent to juxtacrine IL-1α receptor engagement, the SASP depends upon intracellular signaling by the p38MAPK (p38 mitogen-activated protein kinase)-NF-κB (nuclear factor-κB) pathway [27, 37–39] (Fig. 2), although p38MAPK and NF-κB are by no means the sole regulators of the SASP [29, 31]. Of particular significance for our discussion here, the SASP is primarily a delayed response to (epi)genomic damage [40, 41].

The SASP, or at least selected components of the SASP, can have striking autocrine and paracrine effects (Fig. 2). As discussed below, the paracrine effects – the ability of senescent cells to alter the behavior of neighboring cells and the quality of the local tissue environment

– are especially pertinent in the context of cancer and aging. Under some physiological circumstances, the paracrine effects of the SASP can be beneficial. Under others, they can be detrimental.

6. Beneficial effects of the SASP

Because the SASP is primarily a genomic damage response [40, 41], one beneficial function of the SASP may be to enable damaged cells to communicate their compromised state to surrounding cells in the tissue. In addition, the SASP may function to stimulate the regeneration and/or repair of tissues after damage [42, 43]. Consistent with this idea, skin wounding and certain types of liver damage were recently shown to induce cellular senescence in some cells within the damaged tissue. These senescent cells, in turn, appeared to be important for limiting the extent of fibrosis during tissue repair. Interestingly, in both cases, the ability to resolve the fibrotic material, which consists largely of collagen and fibronectin, appears to be due the secretion of matrix metalloproteinases (MMPs) [44, 45], which are prominent components of the SASP [33].

The SASP also includes a number of chemokines and cytokines that can attract and activate cells of the immune system. Because senescent cells also express ligands for cytotoxic immune cells such as natural killer cells, the immune system can specifically target senescent cells and kill them *in vivo* [44, 46]. Thus, the senescence response, through the SASP, includes a mechanism that facilitates the eventual clearance of senescent cells from tissues.

Finally, the SASP includes factors that help reinforce the tumor suppressive senescence growth arrest [27, 30–32]. These factors include the pro-inflammatory cytokines interleukin (IL)-6 and IL-8, the protease inhibitor plasminogen activator inhibitor-1 (PAI-1) and the pleiotropic protein insulin-like growth factor binding protein-7 (IGFBP-7). These secreted proteins act by engaging intracellular signaling mechanisms that activate the tumor suppressor pathways that establish and maintain the senescence growth arrest.

7. Detrimental effects of the SASP

At first glance, it might seem contradictory that a tumor suppressive mechanism, which is clearly beneficial, can also have deleterious effects. However, the evolutionary theory of antagonistic pleiotropy predicts such scenarios – specifically, that there can be processes that are beneficial early in life but detrimental later in life. The basis for this theory is grounded in the observation that for the vast majority of organisms that evolved in environments with high extrinsic hazards (infection, predation, starvation, etc) the force of natural selection declines with age. That is, during much of our evolutionary history, aged individuals comprised an increasingly smaller proportion of the population, and so there was little or no selective pressure to improve phenotypes that manifest only at advanced ages[47, 48]. Thus, cellular senescence may be an example of evolutionary antagonistic pleiotropy, suppressing the development of cancer early in life but driving aging and age-related pathology later in life [4].

As noted earlier, senescent cells are targeted and eliminated by the immune system, yet they are found with increasing frequency in older tissues [49–51]. Why this is so is not clear. One possibility is that the aging immune system, which shows both decrements and derangements in function [52, 53], becomes less capable of clearing senescent cells. In addition, the production of senescent cells may increase with age owing to an age-dependent acceleration of tissue damage – for example, increasing oxidative stress due to progressively more damaged and hence less functional mitochondria [54]. It is also possible that a constant fraction of senescent cells escape immune clearance such that they steadily accumulate with

advancing age. Whatever the case, the chronic presence of cells that secrete numerous proteins with potent biological activities might be predicted to significantly alter tissue structure and the local milieu. Indeed, this appears to be the case.

8. The SASP and age-related degenerative pathology

Senescent cells have clearly been shown to disrupt normal tissue structures and differentiated functions in complex cell culture models. For example, senescent stromal fibroblasts have been shown to derange the normal organization and specialized function (milk production) of mammary epithelial cells [55, 56]. Similar to the effects of senescent cells on fibrosis resolution, the effects on mammary epithelial cells were due in large measure to the MMPs that are secreted by senescent cells.

In addition, local tissue effects of a SASP or specific SASP components have been implicated in a wide variety of age-related pathologies *in vivo* (Fig. 3). For example, the SASP of senescent endothelial cells has been causally implicated in age-related vascular calcification [57], which is a major risk factor for serious cardiovascular disease. The pro-inflammatory SASP of senescent endothelial cells has also been proposed to contribute to cardiovascular disease by initiating and fueling the development of atherosclerotic lesions [35, 58]. Likewise, osteoblasts are thought to undergo age-related cellular senescence owing to the increasing oxidative stress in aged bones [59]. In turn, senescent osteoblasts have been proposed to alter the bone microenvironment, thereby contributing to the development of age-related osteoporosis [59, 60]. Further, the expression of a SASP by astrocytes, which has been documented both in cells that were made senescent in culture as well as cells that were isolated from aged brain tissue, has been proposed to initiate or contribute to neuroinflammation [34, 61]; neuroinflammation is a characteristic of many neurodegenerative diseases, and is thought to cause or exacerbate the age-related decline in both cognitive and motor function.

Possibly more direct evidence that senescent cells contribute to age-related degeneration comes from studies of genetically engineered mice that lack expression of the p16INK4a protein. This protein is a potent activator of the pRB tumor suppressor protein, and a tumor suppressor in its own right [62]. p16INK4a is expressed by most senescent cells, wherein it functions to enforce the senescence growth arrest; in addition, ectopic expression of p16INK4a induces a permanent arrest of cell proliferation with many features of cellular senescence [20]. p16INK4a expression is undetectable or very low in most adult tissues, but expression increases with advancing age [63–65]. p16INK4a is dispensable for embryonic and postnatal development. Accordingly, p16INK4a null mice are phenotypically normal for about the first year of life, after which they begin to develop cancer at an accelerated rate. Recently, the age-dependent increase in p16INK4a expression was linked to the declining proliferative capacity of stem cells in the brain, bone marrow and pancreas [66–68] – all three tissues showed significantly preserved stem cell renewal and tissue function in 1 year old p16INK4a null mice. It was not demonstrated in these studies that the p16INK4a-positive stem cells were in fact senescent, and so it is possible that the p16INK4a- and age-dependent loss of brain, hematopoietic and pancreatic function is due to a process (or processes) other than cellular senescence.

Thus, at present, senescent cells and their secretory phenotype are largely a smoking gun with respect to the degenerative pathologies of aging – they are present at the right times (increasing age) and places (tissues that show age-associated loss of function, and degenerative lesions) (Fig. 3). However, whether cellular senescence plays a causal role in age-related degeneration currently remains a speculation.

9. The SASP and cancer

Although the senescence growth arrest is clearly tumor suppressive, there is mounting evidence that the SASP can promote malignant phenotypes in culture and tumor growth *in vivo* [28, 29, 69–73] (Fig. 3). In culture, the SASP is a potent inducer of an epithelial-to-mesenchyme transition, a critical step in the development of invasive and metastatic carcinoma. This activity is due mainly to the SASP component factors IL-6, IL-8 and GRO (growth-related oncogene)α. GROα is also a robust mitogen, particularly for premalignant epithelial cells, as are a number of other SASP factors. Most importantly, in mouse xenograft studies, senescent cells have been shown to stimulate tumor growth and invasiveness *in vivo*, and this activity is due in part to the secretion of MMPs by senescent cells. It has not yet been demonstrated that senescent cells or the SASP stimulates the progression of naturally occurring tumors. However, the xenograft studies support the idea that -- as both senescent cells and (mutant) premalignant cells accumulate with age [74] -- the SASP of senescent cells might stimulate nearby premalignant cells to progress to full blown malignancy (Fig. 3).

10. The SASP and damage at a distance: a hypothesis

As noted earlier, an important feature of the SASP is that it is primarily a response to genomic or epigenomic damage. That is, cells that are induced to senesce by most stimuli harbor persistent DNA damage and DNA damage signaling, which is required to establish and maintain the SASP [40, 41]. In this regard, growth arrested senescent cells and proliferative cancer cells have a shared phenotype: most cancer cells are genomically unstable and also harbor persistent DNA damage and DNA damage signaling [75, 76]. In light of this similarity, it is perhaps not surprising that cancer cells also tend to secrete numerous factors that modify the tissue microenvironment to facilitate tumor growth [10–13]. Indeed, damaged cells that have bypassed the p16INK4a- and p53-enforced senescence checkpoints and hence proliferate with persistent DNA damage [77] express a secretory phenotype that overlaps significantly with the SASP of senescent cells [29, 33, 40]. Thus, the SASP can more broadly be considered a damage response that is associated with, but not necessarily specific to, the senescence response.

In addition to creating a local tissue milieu that can promote degeneration and/or malignant tumorigenesis (Fig. 3), the SASPs of senescent or damaged cells can, in principle, have systemic effects. Thus, we hypothesize that the accumulation of senescent and/or damaged cells during aging might be a source of mobile factors – particularly pro-inflammatory factors – that drive not only local pathology, but distal pathology as well. For example, the SASPs of senescent or damaged cells in the skin, which increase with age [65, 78, 79], might cause or contribute to the age-related rise in circulating inflammatory cytokines such as IL-6, which, in turn, are thought to promote a variety of chronic degenerative diseases, as well as cancer [80–82]. That is, cellular damage and an accompanying SASP in one tissue might produce systemic factors promote pathology, both degenerative and hyperplastic, in distal tissues. This damage-at-a-distance hypothesis has important implications for how age-related diseases, including cancer, are viewed by both basic scientists and clinicians.

Although there is no direct evidence for this damage-at-a-distance hypothesis with regard to age-related pathologies, there are many examples in the literature of circulating systemic factors that are altered during aging. Moreover, there is evidence that at least some of these alterations can mediate age-related decrements in tissue function. In some cases, most notably skeletal muscle repair and function, beneficial systemic factors appear to be depleted in aged animals [83], whereas in other cases deleterious systemic factors appear to increase in aged animals [84, 85].

Importantly, there is a sparse body of literature that supports the concept that some pathologies can alter the systemic milieu such that apparently unrelated pathologies are exacerbated [86–88]. For example, paraneoplastic neurological syndromes – neurological syndromes of unknown cause that often precede the diagnosis of a cancer that is clearly clinically irrelevant to the neurological symptoms – have long been recognized as rare, but well-documented, complications of malignant tumors; in some cases, elements of this syndrome appear to be due to autoimmune reactions, but, in other cases, the autoantibodies appear to be simply markers and the tumor-derived factors responsible for the syndrome have yet to be identified [87]. In the majority of cancer cases, in which there is no evidence of paraneoplastic neurological syndrome, it is becoming increasingly clear that malignant tumors can actively perturb host organs at distant anatomic sites [12]. Perhaps the most striking example in this regard – and the most relevant for our hypothesis -- is the recent finding in mice that xenografted tumors can cause DNA damage in distal, apparently healthy tissues by virtue of tumor-derived inflammatory factors [89].

The ‘damage at a distance’ hypothesis proposed here has the potential to explain age-related co-morbidities in ways that are not currently considered in the clinic. At present, age-related pathologies are viewed as monolithic entities. Aside from very specific disease manifestations or treatments, cardiologists rarely consider how heart disease might affect the development of cancer, oncologists rarely consider the impact of epithelial tumors on cardiovascular fitness or neurodegeneration, and so forth. Our hypothesis posits that – at least for pathologies that are fueled by damaged or senescent cells – disease states can interact via soluble mediators, although of course physiological and other factors might also contribute to disease interactions. Moreover, our hypothesis identifies the SASP is a promising target for interventions that may target multiple age-related pathologies, both degenerative and neoplastic, simultaneously.

References

1. The Silver Book. Chronic disease and medical innovation in an aging nation. 2009. Updated May 24, 2011; Available from: http://www.silverbook.org/
2. Vijg J, Campisi J. Puzzles, promises and a cure for ageing. Nature. 2008; 454:1065–71. [PubMed: 18756247]
3. Balducci L, Ershler WB. Cancer and ageing: a nexus at several levels. Nature Rev Cancer. 2005; 5:655–62. [PubMed: 16056261]
4. Campisi J. Cancer and ageing: Rival demons? Nature Rev Cancer. 2003; 3:339–49. [PubMed: 12724732]
5. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010; 60:277–300. [PubMed: 20610543]
6. Knudson AG. Chasing the cancer demon. Annu Rev Genet. 2000; 34:1–19. [PubMed: 11092820]
7. Gray JW, Collins C. Genome changes and gene expression in human solid tumors. Carcinog. 2000; 21:443–52.
8. Loeb LA. Human cancers express mutator phenotypes: origin, consequences and targeting. Nature Rev Cancer. 2011; 11:450–7. [PubMed: 21593786]
9. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646–74. [PubMed: 21376230]
10. Bissell MJ, Radisky D. Putting tumours in context. Nature Rev Cancer. 2001; 1:46–54. [PubMed: 11900251]
11. Joyce JA. Therapeutic targeting of the tumor microenvironment. Cancer Cell. 2005; 7:513–20. [PubMed: 15950901]
12. McAllister SS, Weinberg RA. Tumor-host interactions: a far-reaching relationship. J Clin Oncol. 2010; 28:4022–8. [PubMed: 20644094]

13. Liotta LA, Kohn EC. The microenvironment of the tumour-host interface. Nature. 2001; 411:375–9. [PubMed: 11357145]
14. Park CC, Bissell MJ, Barcellos-Hoff MH. The influence of the microenvironment on the malignant phenotype. Molec Med Today. 2000; 6:324–9. [PubMed: 10904250]
15. McCullough D, Coleman WB, Smith GJ, Grisham JW. Age-dependent induction of hepatic tumor regression by the tissue microenvironment after transplantation of neoplastically transformed rat liver epithelial cells into the liver. Cancer Res. 1997; 57:1807–13. [PubMed: 9135026]
16. DePinho RA. The age of cancer. Nature. 2000; 408:248–54. [PubMed: 11089982]
17. Campisi J. Cellular senescence as a tumor-suppressor mechanism. Trends Cell Biol. 2001; 11:27–31.
18. Dimri GP. What has senescence got to do with cancer? Cancer Cell. 2005; 7:505–12. [PubMed: 15950900]
19. Itahana K, Dimri G, Campisi J. Regulation of cellular senescence by p53. Eur J Bioch. 2001; 268:2784–91.
20. Ohtani N, Yamakoshi K, Takahashi A, Hara E. The p16INK4a-RB pathway: molecular link between cellular senescence and tumor suppression. J Med Invest. 2004; 51:146–53. [PubMed: 15460900]
21. Ben-Porath I, Weinberg RA. When cells get stressed: an integrative view of cellular senescence. J Clin Invest. 2004; 113:8–13. [PubMed: 14702100]
22. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. Nature Rev Molec Cell Biol. 2007; 8:729–40. [PubMed: 17667954]
23. Passos JF, Von Zglinicki T. Oxygen free radicals in cell senescence: are they signal transducers? Free Radic Res. 2006; 40:1277–83. [PubMed: 17090417]
24. Serrano M, Blasco MA. Putting the stress on senescence. Curr Opin Cell Biol. 2001; 13:748–53. [PubMed: 11698192]
25. Colavitti R, Finkel T. Reactive oxygen species as mediators of cellular senescence. IUBMB Life. 2005; 57:277–81. [PubMed: 16036611]
26. Blagosklonny MV. Cell cycle arrest is not senescence. Aging. 2011; 3:94–101. [PubMed: 21297220]
27. Acosta JC, O'Loghlen A, Banito A, Guijarro MV, Augert A, Raguz S, Furnagalli M, DaCosta M, Brown C, Popov N, Takastu, Yabuta N, Melamed J, d'Adda di Fagagna F, Bernard D, Hernando E, Gil J. Chemokine signaling via the CXCR2 receptor reinforces senescence. Cell. 2008; 133:1006–18. [PubMed: 18555777]
28. Bavik C, Coleman I, Dean JP, Knudsen B, Plymate S, Nelson PS. The gene expression program of prostate fibroblast senescence modulates neoplastic epithelial cell proliferation through paracrine mechanisms. Cancer Res. 2006; 66:794–802. [PubMed: 16424011]
29. Coppe JP, Patil CK, Rodier F, Sun Y, Munoz D, Goldstein J, Nelson PS, Desprez PY, Campisi J. Senescence-associated secretory phenotypes reveal cell non-automous functions of oncogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008; 6:2853–68. [PubMed: 19053174]
30. Kortlever RM, Higgins PJ, Bernards R. Plasminogen activator inhibitor-1 is a critical downstream target of p53 in the induction of replicative senescence. Nature Cell Biol. 2006; 8:877–84. [PubMed: 16862142]
31. Kuilman T, Michaloglou C, Vredeveld LCW, Douma S, van Doorn R, Desmet CJ, AAL, Mooi WJ, Peeper DS. Oncogene-induced senescence relayed by an interleukin-dependent inflammatory network. Cell. 2008; 133:1019–31. [PubMed: 18555778]
32. Wajapeyee N, Serra RW, Zhu X, Mahalingam M, Green MR. Oncogenic BRAF induces senescence and apoptosis through pathways mediated by the secreted protein IGFBP7. Cell. 2008; 132:363–74. [PubMed: 18267069]
33. Coppe JP, Patil CK, Rodier F, Krtolica A, Beausejour C, Parrinello S, Hodgson G, Chin K, Desprez PY, Campisi J. A human-like senescence-associated secretory phenotype is conserved in mouse cells dependent on physiological oxygen. PLoS ONE. 2010; 5:e9188. [PubMed: 20169192]
34. Salminen A, Ojala J, Kaarniranta K, Haapasalo A, Hiltunen M, Soininen H. Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. Eur J Neurosci. 2011; 34:3–11. [PubMed: 21649759]

35. Erusalimsky JD, Kurz DJ. Cellular senescence in vivo: its relevance in ageing and cardiovascular disease. Exp Gerontol. 2005; 40:634–42. [PubMed: 15970413]
36. Orjalo A, Bhaumik D, Gengler B, Scott GK, Campisi J. Cell surface IL-1α is an upstream regulator of the senescence-associated IL6/IL-8 cytokine network. Proc Natl Acad Sci USA. 2009; 106:17031–6. [PubMed: 19805069]
37. Freund A, Patil PK, Campisi J. p38MAPK is a novel DNA damage response-independent regulator of the senescence-associated secretory phenotype. EMBO J. 2011; 30:1536–48. [PubMed: 21399611]
38. Bhaumik D, Scott GK, Schokrpur S, Patil CK, Orjalo A, Rodier F, Lithgow GJ, Campisi J. MicroRNAs miR-146a/b negatively modulate the senescence-associated inflammatory mediators IL-6 and IL-8. Aging. 2009; 1:402–11. [PubMed: 20148189]
39. Freund A, Orjalo A, Desprez PY, Campisi J. Inflammatory networks during cellular senescence: causes and consequences. Trends Molec Med. 2010; 16:238–48. [PubMed: 20444648]
40. Rodier F, Coppé JP, Patil CK, Hoeijmakers WA, Muñoz DP, Raza SR, Freund A, Campeau E, Davalos AR, Campisi J. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nature Cell Biol. 2009; 11:973–9. [PubMed: 19597488]
41. Rodier F, Munoz DP, Teachenor R, Chu V, Le O, Bhaumik D, Coppe JP, Campeau E, Beausejour C, Kim SH, Davalos AR, Campisi J. DNA-SCARS: Distinct nuclear structures that sustain damage-induced senescence growth arrest and inflammatory cytokine secretion. J Cell Sci. 2011; 124:68–81. [PubMed: 21118958]
42. Campisi J. Cellular senescence: putting the paradoxes in perspective. Curr Opin Genet Dev. 2011; 21:107–12. [PubMed: 21093253]
43. Rodier F, Campisi J. Four faces of cellular senescence. J Cell Biol. 2011; 192:547–56. [PubMed: 21321098]
44. Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, Yee H, Zender L, Lowe SW. Senescence of activated stellate cells limits liver fibrosis. Cell. 2008; 134:657–67. [PubMed: 18724938]
45. Jun JI, Lau LF. The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing. Nature Cell Biol. 2010; 12:676–85. [PubMed: 20526329]
46. Xue W, Zender L, Miething C, Dickins RA, Hernando E, Krizhanovsky V, Cordon-Cardo C, Lowe SW. Senescence and tumour clearance is triggered by p53 restoration in murine liver carcinomas. Nature. 2007; 445:656–0. [PubMed: 17251933]
47. Kirkwood TB, Austad SN. Why do we age? Nature. 2000; 408:233–8. [PubMed: 11089980]
48. Longo VD, Finch CE. Evolutionary medicine: from dwarf model systems to healthy centenarians? Science. 2003; 299:1342–6. [PubMed: 12610293]
49. Adams PD. Healing and hurting: molecular mechanisms, functions and pathologies of cellular senescence. Molec Cell. 2009; 36:2–14. [PubMed: 19818705]
50. Campisi J. Senescent cells, tumor suppression and organismal aging: Good citizens, bad neighbors. Cell. 2005; 120:513–22. [PubMed: 15734683]
51. Tchkonia T, Morbeck DE, Von Zglinicki T, Van Deursen J, Lustgarten J, Scrable H, Khosla S, Jensen MD, Kirkland JL. Fat tissue, aging, and cellular senescence. Aging Cell. 2010; 9:667–84. [PubMed: 20701600]
52. McElhaney JE, Effros RB. Immunosenescence: what does it mean to health outcomes in older adults? Curr Opin Immunol. 2009; 21:418–242. [PubMed: 19570667]
53. Rosenstiel P, Derer S, Till A, Häsler R, Eberstein H, Bewig B, Nikolaus S, Nebel A, Schreiber S. Systematic expression profiling of innate immune genes defines a complex pattern of immunosenescence in peripheral and intestinal leukocytes. Genes Immun. 2008; 9:103–14. [PubMed: 18216864]
54. Melov S, Shoffner JM, Kaufman A, Wallace DC. Marked increase in the number and variety of mitochondrial DNA rearrangements in aging human skeletal muscle. Nucleic Acids Res. 1995; 23:4122–6. [PubMed: 7479075]
55. Parrinello S, Coppe JP, Krtolica A, Campisi J. Stromal-epithelial interactions in aging and cancer: senescent fibroblasts alter epithelial cell differentiation. J Cell Sci. 2005; 118:485–96. [PubMed: 15657080]

56. Tsai KK, Chuang EY, Little JB, Yuan ZM. Cellular mechanisms for low-dose ionizing radiation-induced perturbation of the breast tissue microenvironment. Cancer Res. 2005; 65:6734–44. [PubMed: 16061655]
57. Burton DG, Matsubara H, Ikeda K. Pathophysiology of vascular calcification: Pivotal role of cellular senescence in vascular smooth muscle cells. Exp Gerontol. 2010; 45:819–24. [PubMed: 20647039]
58. Gorenne I, Kavurma M, Scott S, Bennett M. Vascular smooth muscle cell senescence in atherosclerosis. Cardiovasc Res. 2006; 72:9–17. [PubMed: 16824498]
59. Manolagas SC. From estrogen-centric to aging and oxidative stress: A revised perspective of the pathogenesis of osteoporosis. Endocr Rev. 2010; 31:266–300. [PubMed: 20051526]
60. Kassem M, Marie PJ. Senescence-associated intrinsic mechanisms of osteoblast dysfunctions. Aging Cell. 2011; 10:191–7. [PubMed: 21210937]
61. Bitto A, Sell C, Crowe E, Lorenzini A, Malaguti M, Hrelia S, Torres C. Stress-induced senescence in human and rodent astrocytes. Exp Cell Res. 2010; 316:2961–8. [PubMed: 20620137]
62. Gil J, Peters G. Regulation of the INK4b-ARF-INK4a tumour suppressor locus: all for one or one for all. Nature Rev Molec Cell Biol. 2006; 7:667–77. [PubMed: 16921403]
63. Krishnamurthy J, Torrice C, Ramsey MR, Kovalev GI, Al-Regaiey K, Su L, Sharpless NE. Ink4a/Arf expression is a biomarker of aging. J Clin Invest. 2004; 114:1299–307. [PubMed: 15520862]
64. Liu Y, Sanoff HK, Cho H, Burd CE, Torrice C, Ibrahim JG, Thomas NE, Sharpless NE. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. Aging Cell. 2009; 8:439–48. [PubMed: 19485966]
65. Ressler S, Bartkova J, Niederegger H, Bartek J, Scharffetter-Kochanek K, Jansen-Durr P, Wlaschek M. p16 is a robust in vivo biomarker of cellular aging in human skin. Aging Cell. 2006; 5:379–89. [PubMed: 16911562]
66. Janzen V, Forkert R, Fleming H, Saito Y, Waring MT, Dombkowski DM, Cheng T, DePinho RA, Sharpless NE, Scadden DT. Stem cell aging modified by the cyclin-dependent kinase inhibitor, $p16^{INK4a}$. Nature. 2006; 443:421–6. [PubMed: 16957735]
67. Krishnamurthy J, Ramsey MR, Ligon KL, Torrice C, Koh A, Bonner-Weir S, Sharpless NE. $p16^{INK4a}$ induces an age-dependent decline in islet regenerative potential. Nature. 2006; 443:453–7. [PubMed: 16957737]
68. Molofsky AV, Slutsky SG, Joseph NM, He S, Pardal R, Krishnamurthy J, Sharpless NE, Morrison SJ. Increasing *Ink4a* expression decreases forebrain progenitors and neurogenesis during ageing. Nature. 2006; 443:448–52. [PubMed: 16957738]
69. Coppe JP, Kauser K, Campisi J, Beausejour CM. Secretion of vascular endothelial growth factor by primary human fibroblasts at senescence. J Biol Chem. 2006; 281:29568–74. [PubMed: 16880208]
70. Dilley TK, Bowden GT, Chen QM. Novel mechanisms of sublethal oxidant toxicity: induction of premature senescence in human fibroblasts confers tumor promoter activity. Exp Cell Res. 2003; 290:38–48. [PubMed: 14516786]
71. Liu D, Hornsby PJ. Senescent human fibroblasts increase the early growth of xenograft tumors via matrix metalloproteinase secretion. Cancer Res. 2007; 67:3117–26. [PubMed: 17409418]
72. Roninson IB. Oncogenic functions of tumour suppressor p21(Waf1/Cip1/Sdi1): association with cell senescence and tumour-promoting activities of stromal fibroblasts. Cancer Lett. 2002; 179:1–14. [PubMed: 11880176]
73. Krtolica A, Parrinello S, Lockett S, Desprez P, Campisi J. Senescent fibroblasts promote epithelial cell growth and tumorigenesis: A link between cancer and aging. Proc Natl Acad Sci USA. 2001; 98:12072–7. [PubMed: 11593017]
74. Hasty P, Campisi J, Hoeijmakers J, van Steeg H, Vijg J. Aging and genome maintenance: Lessons from the mouse? Science. 2003; 299:1355–9. [PubMed: 12610296]
75. Bartkova J, Horejsi Z, Koed K, Kramer A, Tort F, Zieger K, Guldberg P, Sehested M, Nesland JM, Lukas C, Orntoft T, Lukas J, Bartek J. DNA damage response as a candidate anti-cancer barrier in early human tumorigenesis. Nature. 2005; 434:864–70. [PubMed: 15829956]
76. Halazonetis TD, Gorgoulis VG, Bartek J. An oncogene-induced DNA damage model for cancer development. Science. 2008; 319:1352–5. [PubMed: 18323444]

77. Beausejour CM, Krtolica A, Galimi F, Narita M, Lowe SW, Yaswen P, Campisi J. Reversal of human cellular senescence: roles of the p53 and p16 pathways. EMBO J. 2003; 22:4212–22. [PubMed: 12912919]

78. Dimri GP, Lee X, Basile G, Acosta M, Scott G, Roskelley C, Medrano EE, Linskens M, Rubelj I, Pereira-Smith OM, Peacocke M, Campisi J. A novel biomarker identifies senescent human cells in culture and in aging skin in vivo. Proc Natl Acad Sci USA. 1995; 92:9363–7. [PubMed: 7568133]

79. Jeyapalan JC, Ferreira M, Sedivy JM, Herbig U. Accumulation of senescent cells in mitotic tissue of aging primates. Mech Ageing Dev. 2007; 128:36–44. [PubMed: 17116315]

80. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. Proc Natl Acad Sci USA. 2003; 100:9090–5. [PubMed: 12840146]

81. Maggio M, Guralnik JM, Longo DL, Ferrucci L. Interleukin-6 in aging and chronic disease: a magnificent pathway. J Gerontol A Biol Sci Med Sci. 2006; 61:575–84. [PubMed: 16799139]

82. Naugler WE, Karin M. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. Trends Molec Med. 2008; 14:109–19. [PubMed: 18261959]

83. Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature. 2005; 433:760–4. [PubMed: 15716955]

84. Brack AS, Conboy MJ, Roy S, Lee M, Kuo CJ, Keller C, Rando TA. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science. 2007; 317:807–10. [PubMed: 17690295]

85. Carlson ME, Conboy MJ, Hsu M, Barchas L, Jeong J, Agrawal A, Mikels AJ, Agrawal S, Schaffer DV, Conboy IM. Relative roles of TGF-beta1 and Wnt in the systemic regulation and aging of satellite cell responses. Aging Cell. 2009; 8:676–89. [PubMed: 19732043]

86. Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, Leeuwenburgh C, Pahor M, Manini TM. Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. Ageing Res Rev. 2010; 9:369–83. [PubMed: 20438881]

87. Didelot A, Honnorat J. Update on paraneoplastic neurological syndromes. Curr Opin Oncol. 2009; 21:566–72. [PubMed: 19620862]

88. Ilieva H, Polymenidou M, Cleveland DW. Non-cell autonomous toxicity in neurodegenerative disorders: ALS and beyond. J Cell Biol. 2009; 187:761–72. [PubMed: 19951898]

89. Redon CE, Dickey JS, Nakamura AJ, Kareva IG, Naf D, Nowsheen S, Kryston TB, Bonner WM, Georgakilas AG, Sedelnikova OA. Tumors induce complex DNA damage in distant proliferative tissues in vivo. Proc Natl Acad Sci USA. 2010; 107:17992–7. [PubMed: 20855610]

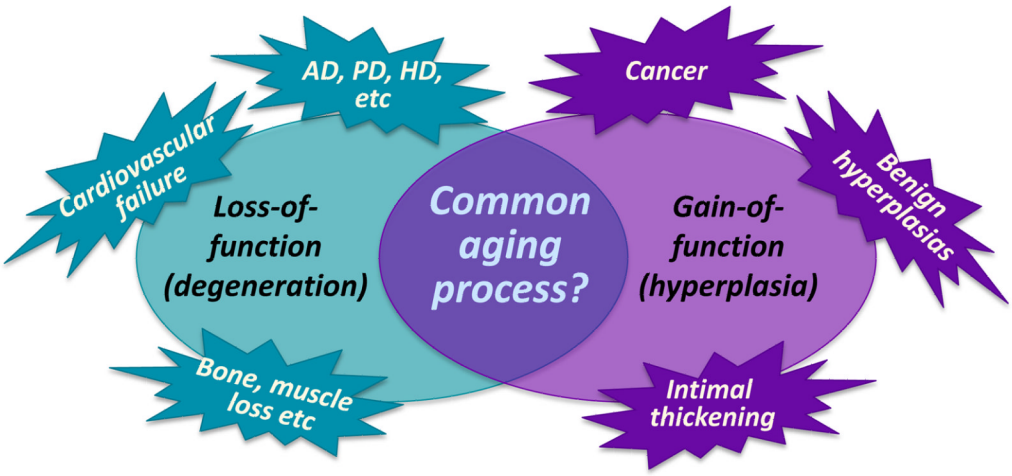

Figure 1.

Relationship among age-related diseases. Age increases the susceptibility to a wide variety of pathologies, which can be binned into two broad categories. The first category, loss-of-function pathologies, are dengenerative in nature, such that cells and tissues lose the ability to function optimally – or to function at all. Examples include neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD), cardiovascular disease, and musculoskeletal decrements (e.g., bone and muscle loss). The second category, gain-of-function pathologies, are generally hyperplastic in nature, such that cells proliferate and/or gain new functions that are deleterious to the organism. Examples include benign hyperplasias such as benign prostatic hyperplasia, the smooth muscle cell hyperproliferation that gives rise to intimal thickening in arterial walls, and, of course, cancer. An important outstanding question is: do the loss-of-function and gain-of-function age-related pathologies have distinct etiologies, or is there a common biology that links all these pathologies of aging?

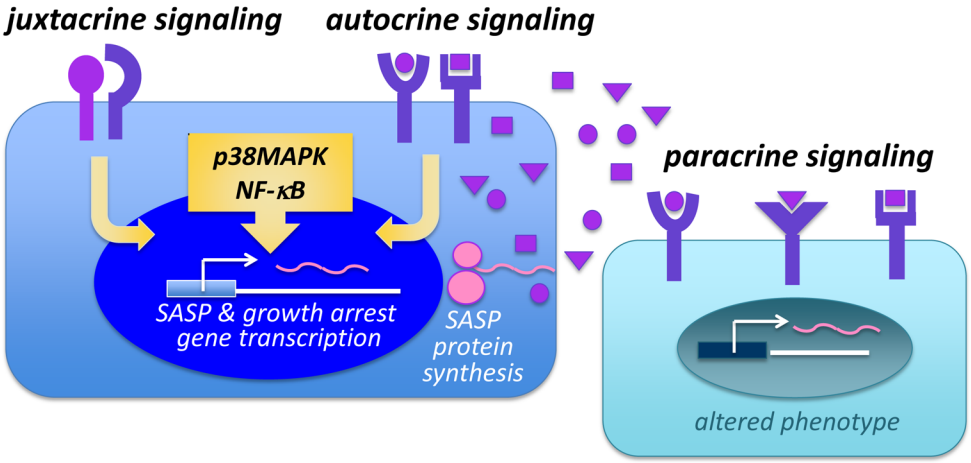

Figure 2.

Signaling mechanisms used by senescent cells. An early event in the senescence response is an increase in the expression of IL-1α, a cytokine that is rarely secreted but rather is membrane-associated where it binds its juxtaposed receptor (juxtacrine signaling). IL-1αreceptor engagement triggers a signaling cascade that ultimately activates the NF-kB transcription factor that transcribes the genes for many of the pro-inflammatory components of the SASP. The senescence response also activates pathways, such as the p38MAPK pathway, which ultimately stimulates the transcription of genes that enforce the senescence growth arrest. SASP components also include secreted factors such as IL-6 and IL-8, which can reinforce the senescence growth arrest by autocrine signaling. Finally, SASP components can markedly affect the behavior of neighboring cells by paracrine signaling.

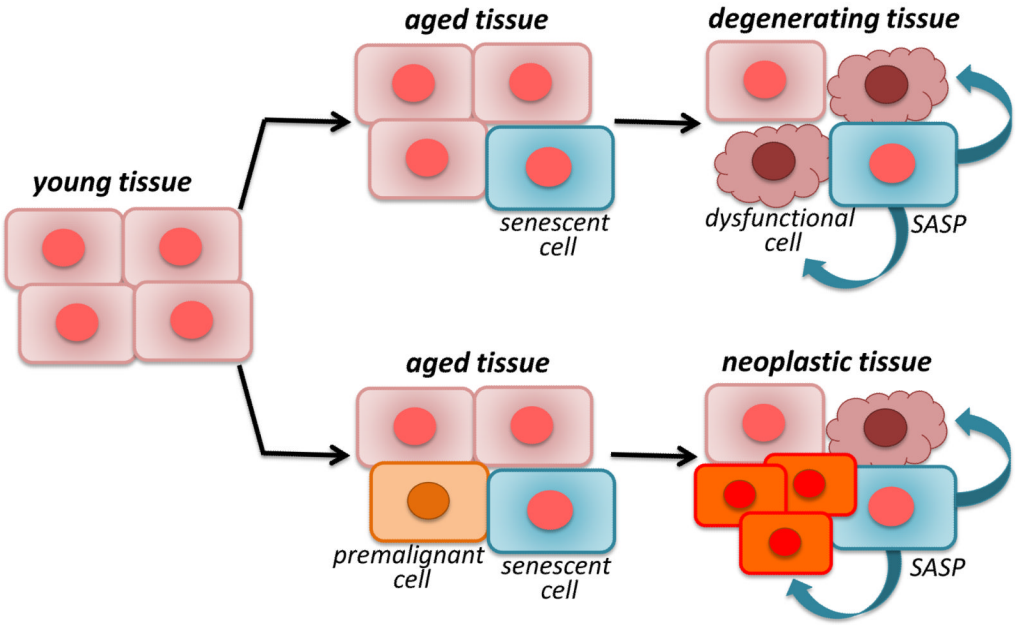

Figure 3.

Senescent cells, by virtue of their SASP, may promote both the degenerative and neoplastic diseases of aging. Both senescent cells and preneoplastic cells increase with age in many tissues. The SASP of senescent cells can cause normal cells within tissues to lose optimal function, leading to tissue degeneration. The SASP can also cause premalignant cells to proliferate and adopt more malignant phenotypes, leading to full-blown cancer.