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

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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 processes 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.

2. Cancer and the degenerative diseases of aging

To begin to understand how multiple diseases of aging might be linked, we have found it 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.

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One variable that promotes a pro-carcinogenic tissue milieu is age [13,14]. However, tissue microenvironments can also acquire the ability to modify the tissue microenvironment, allowing cells to proliferate and survive; this is why tumor cells often tissue microenvironments can suppress the ability of mutant can-
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Disease. For example, cancer progression depends on the senescence response, 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 tumorig-
Fig. 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 degenerative 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?

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 malign-
ant 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 tumorig-

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 oncoproteins, 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-associated secretory phenotype (SASP) is now recognized as a potent and highly efficacious senescence-inducing stimuli. These stimuli include dysfunctional telomeres, non-telomeric DNA damage, disruptions to chromatin organization, the expression of certain activated oncoproteins, 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.

The senescence growth arrest is not simply a halt to cell prolif-
eration, 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 common biology that links all these pathologies of aging?
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 fibropectin, appears to be due to 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 lines 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-mesenchymal 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 invasive 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

![Diagram](image-url)
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 that 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 syndrome, it is becoming increasingly clear that malignant tumors can actively perturb host organs at distant anatomic sites [89]. 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 damage 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 as a promising target for interventions that may target multiple age-related pathologies, both degenerative and neoplastic, simultaneously.

Conflict of interest
None.

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