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Cellular senescence: putting the paradoxes in perspective

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Summary

Cellular senescence arrests the proliferation of potential cancer cells, and so is a potent tumor suppressive mechanism, akin to apoptosis. Or is it? Why did cells evolve an anti-cancer mechanism that arrests, rather than kills, would-be tumor cells? Recent discoveries that senescent cells secrete growth factors, proteases and cytokines provide a shifting view – from senescence as a cell autonomous suppressor of tumorigenesis to senescence as a means to mobilize the systemic and local tissue milieu for repair. In some instances, this mobilization benefits the organism, but in others it can be detrimental. These discoveries provide potential mechanisms by which cellular senescence might contribute to the diverse, and seemingly incongruent, processes of tumor suppression, tumor promotion, tissue repair and aging.

Keywords

Aging; Cancer; Inflammation; Tumor suppression; Wound Healing

Introduction

Cellular senescence was first formally described nearly 5 decades ago as the process that limits the proliferation (growth) of normal human cells in culture [1]. This early study included two prescient -- but seemingly contradictory -- speculations. First, it speculated that the cellular changes associated with the growth arrest might reflect degenerative changes that are hallmarks of organismal aging. Second, it speculated that the senescence growth arrest might suppress the development of cancer *in vivo*.

In the ensuing five decades, remarkable progress has been made in understanding the causes and nature of cellular senescence. There is now substantial evidence that the senescence response suppresses malignant tumorigenesis, and mounting, albeit still indirect, evidence that it can promote aging. Further, recent findings paint an increasingly complex picture of cellular senescence. Under some circumstances, senescent cells can promote tumor progression, in obvious and apparent contradiction to its being tumor suppressive. And under other circumstances, senescent cells appear to aid tissue repair. Emerging data now provide a framework for understanding the strikingly different consequences of cellular senescence, and suggest strategies for harnessing the benefits of this process, while mitigating its potentially deleterious effects.

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Senescent cells – in culture and *in vivo*

Cell culture experiments have identified several hallmarks of senescent cells, which have been used to identify these cells in mammalian tissues. However, there is as yet no single marker or characteristic that is unique to senescent cells. Further, not all senescent cells express all possible senescence markers. Nonetheless, senescent cells can be identified by an aggregate of phenotypes (Fig. 1). Some prominent senescence-associated characteristics are:

1. The classic hallmark of cellular senescence is an essentially irreversible growth arrest, generally in response to potentially oncogenic stimuli [2]. The irreversibility of the arrest -- and fact that senescence is an oncogenic stress response -- distinguish senescent cells from quiescent or terminally differentiated cells.
2. A potent inducer of senescence is (epi)genomic stress, which can result from direct DNA damage, dysfunctional telomeres, disrupted chromatin or strong mitogenic signals, such as those caused by certain oncogenes [2]. These stressors generate persistent DNA damage response (DDR) signals that emanate from stable, cytologically detectable nuclear foci [3] or DNA-SCARS (DNA segments with chromatin alterations reinforcing senescence) [4]. The persistent DDR foci sustain the activity of the p53 tumor suppressor [4,5], which maintains the senescence growth arrest by stimulating the transcription of genes that inhibit cell cycle progression [2].
3. Senescent cells generally adopt an enlarged morphology [1], and express a senescence-associated beta-galactosidase (SA-Bgal) activity that is cytologically detectable in freshly fixed cells or tissues [6].
4. Many senescent cells express p16INK4a, a cyclin-dependent kinase inhibitor and tumor suppressor [7]. p16INK4a is an upstream activator of the pRB tumor suppressor, which, in some cells, orchestrates the formation of cytologically detectable senescence-associated heterochromatin foci (SAHF) [8,9]. These foci silence the expression of genes that are needed for cell cycle progression.
5. Senescent cells that harbor DNA-SCARS secrete numerous cytokines, growth factors and proteases that have wide-ranging autocrine and paracrine activities [10]. This senescence-associated secretory phenotype (SASP), as discussed below, is key to understanding many of the diverse effects attributed to senescent cells.

Most division-competent cells, including some tumor cells, can undergo senescence when appropriately stressed [2,11]. Further, the senescence-associated characteristics and markers described above (Fig. 1) have been used to identify senescent cells in a variety of mammalian tissues. So, when and where are these cells found?

Cellular senescence and aging

The first studies of cellular senescence *in vivo* showed that senescent cells increase with age (Fig. 1), support one of the two prescient early speculations. The increase in senescent cells occurs mainly in tissues that contain mitotically competent cells, and has now been documented in many rodent, non-human primate and human tissues [e.g., see 6,12–14]. Moreover, senescent cells have been identified at sites of several degenerative age-related pathologies (Fig. 1) – examples include atherosclerosis, renal tubulointerstitial fibrosis and glomerulosclerosis, osteoarthritis, slow healing venous ulcers, and degenerating intervertebral discs [13,15–18]. Do senescent cells reflect the aging process and/or the development of age-related pathology? Or do they play causative roles in aging and/or age-related disease? At present, there are no definitive answers to these questions. It has not yet been possible, for example, to eliminate senescent cells and demonstrate improved tissue

function or amelioration of age-related pathology. Nonetheless, recent data suggest two mechanisms by which cellular senescence might actively drive aging and age-related pathology.

First, most adult stem cells are capable of undergoing senescence, and cellular senescence may account at least in part for the age-related decline in the number and/or function of certain stem cells in adult organisms [19–23]. Thus, an accumulation of senescent stem cells may contribute to the decline in tissue repair and regeneration that is a hallmark of aging organisms. Second, the SASP includes factors that control many vital processes within tissues – cell growth, motility and differentiation, as well as tissue structure and vascularization [24,25] (Table 1). Factors secreted by senescent cells might therefore disrupt normal tissue structures and functions [26], including stem cell niches [27]. Finally, the SASP also includes many potent inflammatory cytokines and mediators of inflammatory reactions [28,29] (Table 1). This aspect of the SASP is noteworthy because a widespread feature of aging tissues is low-level chronic inflammation, without obvious microbial infection; furthermore, inflammation is an established cause or contributor to virtually every major age-related disease, both degenerative and hyperproliferative [30,31]. It is therefore possible that senescent cells are a source of the ‘sterile’ inflammation that is a hallmark of aging tissues and driver of multiple age-related pathologies.

Cellular senescence and tumor suppression

Senescent cells have also been found in hyperplastic lesions such as benign prostatic hyperplasia [32], premalignant lesions such as melanocytic nevi and lung adenomas [33,34], and early stage malignancies such as non-invasive pancreatic and prostate cancers [34,35]. Of course, cancer is primarily an age-related disease, despite having characteristics that are quite distinct from the degenerative diseases of aging. Does the presence of senescent cells in pre/early-cancers have functional significance? In this case, the answer is clearly yes. As discussed below, mounting evidence strongly supports the early speculation that cellular senescence is a tumor suppressive mechanism.

First, it is firmly established that mutations that inactivate either the p53 or pRB pathway – both of which are critical for a proper senescence response (Fig. 1) – greatly increase the susceptibility to developing cancer in mice and humans [2,7,36]. Second, although senescent cells are often prominent in premalignant or early cancer lesions, they are rarely found in the aggressive cancers that eventually develop from these lesions [34,35]. In addition, genotoxic chemotherapy can induce a senescence response in some tumor cells, and this response is associated with a cessation of tumor growth and eventual regression [11,37]. Third, and perhaps most importantly, dismantling the senescence response – for example, by inactivating p53 – markedly accelerates the development of malignant tumors from premalignant lesions [35].

It is generally assumed that the growth arrest is the major mechanism by which cellular senescence suppresses malignant tumorigenesis [2,7,36,38]. This is undoubtedly the case. However, there is also evidence that some of the factors secreted by senescent cells help reinforce the senescence growth arrest in an autocrine manner [39–42]. These factors include the pro-inflammatory cytokines IL (interleukin)-6 and IL-8, but also factors such as the pro-apoptotic protein IGFBP (insulin-like growth factor binding protein)-7 and PAI (plasminogen activator inhibitor)-1 (Table 1).

There are now numerous examples of the senescence response acting to suppress cancer progression in both mice and humans [38]. It was somewhat surprising, then, when evidence emerged showing that senescent cells might also *promote* cancer progression.

Cellular senescence and tumor promotion

Cancer is among the pathologies that are fueled by inflammation [43]. Thus, the inflammatory cytokines that comprise the SASP could, in principle, also contribute to the development of age-related cancer by stimulating inflammation. In addition, the SASP includes factors that can induce -- in neighboring cells -- phenotypes that are associated with aggressive cancer cells [10,25] (Table 1). Examples of such SASP factors include amphiregulin and GRO (growth-related oncogene)- α , which stimulate cell proliferation; VEGF (vascular endothelial growth factor), which stimulates angiogenesis; and the pro-inflammatory cytokines IL-6 and IL-8, which can induce an epithelial-to-mesenchyme transitions and epithelial cell migration and invasion.

More direct evidence for tumor promoting effects of senescent cells comes from mouse xenograft experiments in which senescent stromal cells are co-injected with premalignant, or even frankly malignant, epithelial cells. In these studies, senescent cells, but not their non-senescent counterparts, stimulate tumor progression and tumor growth [24,44–46]. In at least one case, the tumor promoting effects of senescence cells could be attributed to their secretion of matrix metalloproteinases (MMPs) [45], which are prominent SASP components [24]. It is not yet known whether senescent cells stimulate the progression of naturally occurring tumor *in vivo*, but at least in mouse xenografts they are clearly capable of promoting the malignant progression of precancerous cells, as well as established tumor cells.

Cellular senescence and tissue repair

A quick glance at the factors that comprise the SASP reveals many proteins that are important for wound healing, tissue repair or tissue regeneration [24,25]. Two recent studies show that senescent cells can indeed participate in repair or regenerative processes *in vivo* in mice.

In one case, acute liver injury stimulated hepatic stellate cells to proliferate and produce an extracellular matrix-rich fibrotic scar; the stellate cells subsequently underwent senescence, accompanied by the secretion of MMPs and dissolution of the fibrotic scar [47]. When stellate cells were rendered incapable of undergoing senescence (due to genetic deficiency in either the p53 or pRB pathways), the liver injury resulted in severe fibrosis that did not resolve. Thus, at least in this model, the senescence response was important for limiting the extent of fibrosis after tissue damage. In a second case, skin the extracellular matrix protein CCN1 was expressed in skin wounds and induced a senescence response in resident fibroblasts and myofibroblasts [48]. Mice engineered to express a CCN1 protein that fails to bind fibroblasts and induce senescence developed excessive fibrosis during wound healing, presumably due to the deficiency in MMPs at the site of the wound.

These findings suggest that senescent cells, and particularly the SASP, may function to communicate cellular damage or dysfunction to the surrounding tissue, and stimulate repair.

Reconciling the apparent paradoxes

Two processes to which cellular senescence contributes (tumor suppression and tissue repair) are clearly beneficial, whereas two others (aging and tumor promotion) are clearly detrimental (Fig. 2). How can these apparently paradoxical activities be reconciled?

A teleological answer to this question is provided by theories that explain the evolution of late life phenotypes [49]. Most organisms evolve in environments that are rich in fatal extrinsic hazards (starvation, infection, predation, etc). In such environments, old individuals

are rare. Consequently, selection against processes that promote late life disabilities is weak. Thus, evolutionary theory holds that aging phenotypes, including age-related disease, are a consequence of the declining force of natural selection with age. An extension of this theory is the concept of antagonistic pleiotropy [49]: a biological process that was selected to promote fitness in young organisms (for example, a tumor suppressive mechanism) can be deleterious in old organisms (for example, promote age-related disease, including late life cancer).

From the evolutionary arguments and documented biological activities of cellular senescence, we hypothesize that the senescence response evolved to both suppress the development of cancer and promote tissue repair in young organisms (Fig. 2). This idea suggests that cellular senescence is not simply a tumor suppressive failsafe mechanism, redundant to apoptosis. Rather, it may also be an important response for resolving tissue damage. A role for senescence in tissue repair would also explain the evolution of the SASP and the finding that senescence-associated inflammatory cytokine secretion is controlled by DDR signaling [5]. The dark side (unselected activities) of the senescence response, then, would be revealed only late in life, when the age-dependent accumulation of senescent cells could create local sites of chronic inflammation, tissue remodeling and other features of wound healing – which are also known to promote the development of cancer (Fig. 2).

Conclusions

There are now at least four major processes to which cellular senescence is thought to contribute– tumor suppression, aging, tumor promotion and tissue repair (Fig. 2). The apparent paradox -- that two of these processes benefit the organism, whereas two of the processes compromise organismal fitness – can be reconciled by understanding how aging phenotypes evolved. And the apparent redundancy to apoptosis as a tumor suppressive mechanism and secretory phenotype of senescent cells can be understood if the senescence response evolved to allow damaged cells to communicate their compromised state to the surrounding tissue and prepare the tissue for repair.

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Abbreviations

DDR	DNA damage response
DNA-SCARS	DNA segments with chromatin alterations reinforcing senescence
MMP	Matrix metalloproteinase
SA-Bgal	Senescence-associated beta-galactosidase
SAHF	Senescence-associated heterochromatin foci
SASP	Senescence-associated secretory phenotype

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Figure 1. Characteristics and documented presence of senescent cells

Potentially oncogenic stimuli induce cellular senescence via activation of the p53 and pRB tumor suppressor pathways. The senescent phenotype develops over several days in culture, and, depending on the type of cell and stimulus, includes expression of SA-Bgal activity and p16INK4a, development of DNA-SCARS that provide continuous DDR signals and SAHF, and the expression of a SASP. To varying extents, these senescence-associated characteristics have been used to identify senescent cells *in vivo* in mouse, non-human primate and human tissues. Conditions under which senescence cells have been identified *in vivo* include normal aging, damaged or wounded tissues, degenerative pathologies of aging, and hyperplastic, preneoplastic and early neoplastic lesions.

Figure 2. Selected and unselected activities of senescent cells

Cellular senescence contributes to four biological processes through the cell autonomous growth arrest and paracrine activities of the SASP. We hypothesize that the growth arrest and SASP are selected traits that ensure tumor suppression and facilitate tissue repair, respectively. However, the SASP also has unselected activities that can cause or contribute to tumor promotion and aging.

Table 1

Autocrine and paracrine activities of selected SASP factors

Factor	Symbol	Major Activities
Amphiregulin	AREG	Cell proliferation
Granulocyte-macrophage colony stimulating factor	GM-CSF	Hematopoietic stem cell differentiation; inflammation
Growth-related oncogene(s) (CXC chemokines)	GROs CXCLs	Cell proliferation; cell migration/invasion
Insulin-like growth factor binding protein-7	IGFBP-7	Apoptosis; autocrine growth arrest
Interleukin-6	IL-6	Epithelial-to-mesenchyme transition; cell migration/invasion; inflammation; autocrine growth arrest
Interleukin-8	IL-8 CXCL8	Epithelial-to-mesenchyme transition; cell migration/invasion; inflammation; autocrine growth arrest
Matrix metalloproteinase(s)	MMPs	Tissue remodeling; cell migration/invasion; wound healing (resolution of fibrosis)
Monocyte chemoattractant proteins (CCL chemokines)	MCPs CCLs	Inflammation; cell migration/invasion
Plasminogen activator inhibitor-1	PAI-1	Wound healing; autocrine growth arrest
Vascular endothelial growth factor	VEGF	Endothelial cell migration/invasion; angiogenesis