Four faces of cellular senescence

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Cellular senescence is an important mechanism for preventing the proliferation of potential cancer cells. Recently, however, it has become apparent that this process entails more than a simple cessation of cell growth. In addition to suppressing tumorigenesis, cellular senescence might also promote tissue repair and fuel inflammation associated with aging and cancer progression. Thus, cellular senescence might participate in four complex biological processes (tumor suppression, tumor promotion, aging, and tissue repair), some of which have apparently opposing effects. The challenge now is to understand the senescence response well enough to harness its benefits while suppressing its drawbacks.

Introduction

Cellular senescence was formally described more than 40 years ago as a process that limited the proliferation (growth) of normal human cells in culture (Hayflick, 1965). This landmark paper contained two prescient statements. The first statement was “unlimited cellular division or . . . escape from senescent-like changes . . . can only be achieved by [somatic] cells which have . . . assumed properties of cancer cells.” The second was “the [cessation of cell growth in culture] may be related to senescence [aging] in vivo.” Thus, nearly half a century ago, the process now known as cellular senescence was linked to both tumor suppression and aging.

In the ensuing decades, we learned much about what causes cellular senescence and the nature of the senescent phenotype. Importantly, we are beginning to understand its physiological relevance. Recent data validate the early idea that cellular senescence is important for tumor suppression. The data now also strongly suggest that cellular senescence contributes to aging, and, further, that senescence-associated phenotypes can contribute to both tumor progression and normal tissue repair. They also offer insights into why, beyond the simple growth arrest, the complex senescent phenotypes may have evolved.

Cellular senescence: a primer

Cellular senescence refers to the essentially irreversible growth arrest that occurs when cells that can divide encounter oncogenic stress. With the possible exception of embryonic stem cells (Miura et al., 2004), most division-competent cells, including some tumor cells, can undergo senescence when appropriately stimulated (Shay and Roninson, 2004; Campisi and d’Adda di Fagagna, 2007).

What causes cellular senescence? Senescence-inducing stimuli are myriad. We now know that the limited growth of human cells in culture is due in part to telomere erosion, the gradual loss of DNA at the ends of chromosomes (telomeres). Telomeric DNA is lost with each S phase because DNA polymerases are unidirectional and cannot prime a new DNA strand, resulting in loss of DNA near the end of a chromosome; additionally, most cells do not express telomerase, the specialized enzyme that can restore telomeric DNA sequences de novo (Harley et al., 1990; Bodnar et al., 1998). We also know that eroded telomeres generate a persistent DNA damage response (DDR), which initiates and maintains the senescence growth arrest (d’Adda di Fagagna et al., 2003; Takai et al., 2003; Herbig et al., 2004; Rodier et al., 2009, 2011). In fact, many senescent cells harbor genomic damage at nontelomeric sites, which also generate the persistent DDR signaling needed for the senescence growth arrest (Nakamura et al., 2008). DNA double strand breaks are especially potent senescence inducers (DiLeonardo et al., 1994). In addition, compounds such as histone deacetylase inhibitors, which relax chromatin without physically damaging DNA, activate the DDR proteins ataxia telangiectasia mutated (ATM) and the p53 tumor suppressor (Bakkenist and Kastan, 2003), and induce a senescence response (Ogryzko et al., 1996; Munro et al., 2004). Finally, many cells senesce when they experience strong mitogenic signals, such as those delivered by certain oncogenes or highly expressed pro-proliferative genes (Serrano et al., 1997; Lin et al., 1998; Zhu et al., 1998; Dimri et al., 2000). Notably, these mitogenic signals can create DNA damage and a persistent DDR due to misfired replication origins and...
Senescent cells increase in size, sometimes enlarging more than twofold relative to the size of nonsenescent counterparts (Hayflick, 1965).

Senescent cells express a senescence-associated β-galactosidase (SA-Bgal; Dimri et al., 1995), which partly reflects the increase in lysosomal mass (Lee et al., 2006).

Most senescent cells express p16INK4a, which is not commonly expressed by quiescent or terminally differentiated cells (Alcorta et al., 1996; Hara et al., 1996; Serrano et al., 1997; Brenner et al., 1998; Stein et al., 1999). In some cells, p16INK4a, by activating the pRB tumor suppressor, causes formation of senescence-associated heterochromatin foci (SAHF), which silence critical pro-proliferative genes (Narita et al., 2003). p16INK4a, a tumor suppressor, is induced by culture stress and as a late response to telomeric or intrachromosomal DNA damage (Brenner et al., 1998; Robles and Adami, 1998; Ramirez et al., 2001; te Poele et al., 2002; Jacobs and de Lange, 2004; Le et al., 2010). Moreover, p16INK4a expression increases with age in mice and humans (Zindy et al., 1997; Nielsen et al., 1999; Krishnamurthy et al., 2004; Ressler et al., 2006; Liu et al., 2009), and its activity has been functionally linked to the reduction in progenitor cell number that occurs in multiple tissues during aging (Janzen et al., 2006; Krishnamurthy et al., 2006; Molofsky et al., 2006).

Cells that senesce with persistent DDR signaling harbor persistent nuclear foci, termed DNA segments with chromatin alterations reinforcing senescence (DNA-SCARS). These foci contain activated DDR proteins, including phospho-ATM and phosphorylated ATM/ataxia telangiectasia and Rad3 related (ATR) substrates (d’Adda di Fagagna et al., 2003; Herbig et al., 2004; Rodier et al., 2009), and are distinguishable from transient damage foci (Rodier et al., 2011). DNA-SCARS include dysfunctional telomeres or telomere dysfunction–induced foci (TIF; d’Adda di Fagagna et al., 2003; Takai et al., 2003; Herbig et al., 2004; Kim et al., 2004).

**Figure 1. Hallmarks of senescent cells.** Senescent cells differ from other nondividing (quiescent, terminally differentiated) cells in several ways, although no single feature of the senescent phenotype is exclusively specific. Hallmarks of senescent cells include an essentially irreversible growth arrest; expression of SA-Bgal and p16INK4a; robust secretion of numerous growth factors, cytokines, proteases, and other proteins (SASP); and nuclear foci containing DDR proteins (DNA-SCARS/TIF) or heterochromatin (SAHF). The pink circles in the nonsenescent cell (left) and senescent cell (right) represent the nucleus.
from these lesions (Bartkova et al., 2005; Michaloglou et al., 2005). Likewise, in mouse models of oncogenic Ras expression or Pten deletion, senescent cells were abundant in premalignant lesions, but scarce in the cancers that eventually developed (Braig et al., 2005; Chen et al., 2005; Collado et al., 2005). Further, dismantling the senescence response by inactivating p53 caused a striking acceleration in the development of malignant tumors (Chen et al., 2005).

In addition, some tumor cells retain the ability to senesce (Shay and Roninson, 2004), and do so in vivo in response to chemotherapy (Schmitt et al., 2002; Coppé et al., 2010) or, in some tissues, after reactivation of p53 (Ventura et al., 2007; Xue et al., 2007). In these cases, the senescence response is associated with tumor regression. Of note, the regressing tumor elicits an inflammatory response that stimulates the innate immune system, which eliminates the senescent cells. As we discuss in subsequent sections, the generation of local inflammation may explain other biological activities of senescent cells.

Although it is clear that cellular senescence arrests incipient tumors at a premalignant stage, it is not clear how tumors eventually, albeit infrequently, emerge from these lesions. Do they arise from senescent cells in which mutations, epigenetic changes, or signals from the tissue reverse the senescence growth arrest? Or do they arise from nonsenescent cells in the premalignant lesion that are dormant or temporarily unable to proliferate and eventually bypass apoptosis or senescence? Whatever the case, the examples above, and a growing list of similar studies (Collado and Serrano, 2010), argue that cellular senescence restrains cancer by imposing a cell-autonomous block to the proliferation of oncogenically damaged/stressed cells (Fig. 2).

It was surprising, then, to learn that senescent cells also can promote cancer progression. As discussed in the next section, this activity derives largely from cell nonautonomous mechanisms.

Cellular senescence and tumor suppression

It is now clear that cellular senescence is a crucial anticancer mechanism that prevents the growth of cells at risk for neoplastic transformation.

The stimuli that elicit a senescence response all have the potential to initiate or promote carcinogenesis. Moreover, to form a lethal tumor, cancer cells must acquire a greatly expanded growth potential and ability to proliferate while expressing activated oncogenes (Hanahan and Weinberg, 2000), traits that are suppressed by the senescence program. Further, cellular senescence depends critically on two powerful tumor suppressor pathways: the p53 and pRB/p16INK4a pathways (Hara et al., 1991; Shay et al., 1991; Bond et al., 1994; Lin et al., 1998; Schmitt et al., 2002; Beauséjour et al., 2003; Collins and Sedivy, 2003; Oren, 2003; Herbig et al., 2004; Jacobs and de Lange, 2004; Ohtani et al., 2004; Chen et al., 2005; Campisi and d'Adda di Fagagna, 2007; Rodier et al., 2007). Both pathways integrate multiple aspects of cellular physiology to determine and orchestrate cell fate. In humans and mice, most, if not all, cancers harbor mutations in one or both these pathways. Moreover, defects in either pathway compromise cellular ability to undergo senescence, and greatly increase organismal susceptibility to cancer.

Studies of human tissues and cancer-prone mice argue strongly that cellular senescence suppresses cancer in vivo. Premalignant human nevi and colon adenomas contained cells that express senescence markers, including SA-Bgal and DDR signaling; however, senescent cells were markedly diminished in the malignant melanomas and adenocarcinomas that develop from these lesions (Bartkova et al., 2005; Michaloglou et al., 2005). Likewise, in mouse models of oncogenic Ras expression or Pten deletion, senescent cells were abundant in premalignant lesions, but scarce in the cancers that eventually developed (Braig et al., 2005; Chen et al., 2005; Collado et al., 2005). Further, dismantling the senescence response by inactivating p53 caused a striking acceleration in the development of malignant tumors (Chen et al., 2005).

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**Cellular senescence and tumor promotion**

At first glance, the idea that cellular senescence, an established anticancer mechanism, can promote cancer seems paradoxical.
However, the evolutionary theory of antagonistic pleiotropy stipulates that a biological process can be both benefit- 
acular and deleterious, depending on the age of the organism (Williams, 1957; 
Rauser et al., 2006). It is important to remember that cancer is 
primarily an age-related disease (Campisi, 2003; Balducci and 
Ershler, 2005). Age is the largest single risk factor for develop-
ing a malignant tumor, and cancer incidence rises approximately 
exponentially after about age 50 (in humans). In these respects, 
cancer is very similar to the degenerative diseases of aging.

The rationale for antagonistic pleiotropy rests on the fact 
that most organisms evolve in environments that are replete 
with fatal extrinsic hazards (predation, infection, starvation, 
etc.). Under these conditions, aged individuals are rare, and so 
selection against processes that promote late-life disability or 
disease is weak. That is, age-associated phenotypes, including 
age-related diseases, have escaped the force of natural selec-
tion. Thus, a biological process that was selected to promote 
fitness in young organisms (e.g., suppressing cancer) can be 
detrimental in aged organisms (promoting late-life disease, 
including cancer).

Why might cellular senescence be antagonisti-
cally pleiotropic? More specifically, how might the senes-
cence response promote late-life cancer? There are as yet no 
definitive answers to these questions. However, recent evidence 
supports the idea that senescent cells can at least in principle 
fuel cancer, and provides a potential mechanism by which this 
might occur.

First, senescent cells increase with age in a variety of 
mammalian tissues (Dimri et al., 1995; Paradis et al., 2001; 
Melk et al., 2003; Erusalinsky and Kurz, 2005; Jeyapalan et al., 
2007; Wang et al., 2009). It is not known whether this rise is 
caused by increased generation, decreased elimination, or both. 
Whatever the genesis, the age-related increase in senescent cells 
occurs in mitotically competent tissues, which, of course, are 
those that give rise to cancer.

Second, as noted in the section on what defines a senes-
cent cell, senescent cells develop a secretory phenotype (SASP) 
that can affect the behavior of neighboring cells. Strikingly, 
many SASP factors are known to stimulate phenotypes associ-
ated with aggressive cancer cells. For example, senescent fibro-
blasts secrete amphieregulin and growth-related oncogene 
(GRO) α, which, in cell culture models, stimulate the proliferation 
of premalignant epithelial cells (Bavik et al., 2006; Coppé et al., 
2010). Senescent cells also secrete high levels of interleukin 6 
(IL-6) and IL-8, which can stimulate premalignant and weakly 
malignant epithelial cells to invade a basement membrane 
(Coppé et al., 2008). Further, senescent fibroblasts and meso-
thelial cells secrete VEGF (Coppé et al., 2006; Ksiazek et al., 
2008), which stimulates endothelial cell migration and invasion 
(a critical step in tumor-initiated angiogenesis), and senescent 
fibroblasts and keratinocytes secrete matrix metalloproteinases 
(MMPs; Millis et al., 1992; Kang et al., 2003; Coppé et al., 
2010), which facilitate tumor cell invasiveness. So, do senes-
cent cells stimulate or inhibit tumorigenesis in vivo?

Senescent cells can stimulate tumorigenesis in vivo. It is not yet known whether naturally occurring 
senescent cells stimulate the progression of naturally occurring 
tumors in vivo. However, senescent, but not nonsenescent, fibro-
blasts stimulate premalignant epithelial cells, which do not ordinar-
ily form tumors, to form malignant cancers when the two cell types 
are co-injected into mice (Krtolica et al., 2001). Further, co-
injection of senescent, but not nonsenescent, cells with fully 
malignant cancer cells markedly accelerates the rate of tumor 
formation in mice (Krtolica et al., 2001; Liu and Hornsby, 2007; 
Bhatia et al., 2008; Bartholomew et al., 2009; Coppé et al., 
2010). Thus, at least in mouse xenografts, senescent cells have 
been shown to promote malignant progression of precancerous, 
as well as established cancer cells, in vivo (Fig. 2). In the future, 
a more critical test of the idea that senescent cells can promote 
the development of cancer, especially the progression of age-
related cancers, will require strategies to eliminate senescent 
cells or effects of the SASP from cancer-prone tissues in vivo.

Although paracrine activities of many SASP proteins can 
promote phenotypes associated with malignancy, the SASP is 
complex and thus not all components are cancer promoting. For 
example, senescent keratinocytes secrete the anti-angiogenic 
factor maspin (Nickoloff et al., 2004). Further, senescent human 
melanocytes secrete IGFBP7, which induces senescence in a 
fraction of nonsenescent melanocytes and apoptosis in certain 
melanoma cell lines (Wajapeeyee et al., 2008), at least in some 
cases (Decarlo et al., 2010). In addition, each SASP factor may 
have effects that depend on the cell and tissue context. For 
example, the IL-6, IL-8, and plasminogen activator inhibitor-1 
(PAI-1) that are secreted by senescent fibroblasts can promote 
tumor suppression by reinforcing the senescence growth arrest 
induced by activated oncogenes or oxidative stress (Fig. 2; 
Kortlever et al., 2006; Acosta et al., 2008; Kuilman et al., 2008). 
However, IL-6 and IL-8 have also been shown to promote ma-
lignant tumorigenesis in cooperation with certain activated on-
cogenes (Sparmann and Bar-Sagi, 2004; Ancrile et al., 2007).

Cellular senescence and aging
Cancer is an age-related disease, but differs from most other 
age-related pathologies in at least one fundamental aspect. To 
form a lethal tumor, cancer cells must acquire new, albeit aber-
rant, phenotypes (Hanahan and Weinberg, 2000). In contrast, for 
most age-related diseases, normal cellular/tissue functions fail. 
Thus, most age-related pathologies are degenerative, whereas 
cancer can hardly be considered a degenerative disease. Does 
cellular senescence, then, contribute to aging and age-related 
diseases other than cancer? There is mounting, although not yet 
definitive, evidence that the answer to this question is yes.

Altered p53 function and aging. Among the more 
compelling evidence that senescent cells can drive degener-
ating aging pathologies are the phenotypes of transgenic mice 
with hyperactive p53. Several years ago, two landmark papers 
described mouse models in which constitutive expression of an 
artificially (Tyner et al., 2002) or naturally (Maier et al., 2004) 
truncated p53 protein resulted in chronically elevated p53 activ-
ity. These mice were exceptionally cancer-free, which was not 
surprising, as p53 is a critical tumor suppressor. What was sur-
prising was their shortened life span and premature aging. Like 
all progeroid models, these mice did not completely phenocopy 
normal aging. Nonetheless, between the two models, the mice
showed premature degenerative changes, including loss of fertility, osteoporosis, sarcopenia, dermal thinning, loss of subcutaneous fat, reduced hair growth, and retarded wound healing. Notably, cells from these mice underwent rapid senescence in culture (Maier et al., 2004). Moreover, tissues from these mice rapidly accumulated senescent cells, and, in lymphoid tissue, the p53 response shifted from primarily apoptotic to primarily senescent in vivo (Hinkal et al., 2009). Thus, there was a strong correlation between excessive cellular senescence and premature aging phenotypes.

It should be noted that another mouse model of elevated p53 activity showed unusual cancer resistance but normal longevity, with no signs of premature aging (García-Cao et al., 2002). In this model, extra copies of the wild-type p53 locus were introduced into the mouse genome. So, rather than being constitutively expressed, p53 was regulated normally, reaching higher levels only upon activation. This heightened p53 activation synergized with other transgenes to extend mean life span (Matheu et al., 2004, 2007; Tomás-Loba et al., 2008), thus p53 can be pro-aging or pro-longevity, depending on the physiological context (de Keizer et al., 2010).

Other gene functions and aging. Other mouse models also suggest that cellular senescence can drive age-related pathologies other than cancer.

One example is conditional ablation of a single allele encoding the p53-related protein p63, which caused extensive cellular senescence and multiple age-related pathologies (Keyes et al., 2005). Another example is mice that express a hypomorphic form of the mitotic checkpoint protein BubR1. These mice experience genotoxic stress, which induced widespread cellular senescence and several age-related degenerative pathologies; further, genetic manipulations that attenuated (p16INK4a deficiency) or exacerbated (deficiency in p19ARF) the senescence response also attenuated or exacerbated the pathology (Baker et al., 2008). Likewise, a mouse model of Hutchinson-Gilford progeria syndrome (HGPS), a childhood premature aging syndrome caused by aberrant lamin A processing, developed phenotypes that overlap with those of HGPS children and do not include cancer; cells from these mice showed chronic DDR signaling, chronic p53 activation, and cellular senescence (Varela et al., 2005). Further, administration of drugs such as statins and aminobisphosphonates reduced DDR signaling in the cells, and also alleviated some of the progeroid symptoms in the mice (Varela et al., 2008). In all these (and other) models of both accelerated and normal aging, it is important to note that the crucial roles for the p53 and/or p16INK4a/pRB pathways are not singular. There is mounting evidence that these pathways interact and modulate each other (Zhang et al., 2006; Leong et al., 2009; Su et al., 2009; Yamakoshi et al., 2009).

Finally, mouse models without obvious activated DDR signaling also suggest that senescent cells can drive aging phenotypes. One example is mice that lack CHIP (carboxy terminal of Hsp70-interacting protein), a chaperone/ubiquitin ligase that helps eliminate damaged proteins. CHIP-deficient animals rapidly accumulate senescent cells, and rapidly develop age-related phenotypes, including thin skin and loss of adiposity and bone density (Min et al., 2008). Likewise, mice that lack the circulating hormone Klotho age prematurely (Kuro-o et al., 1997). The primary cause of the progeroid phenotypes of Klotho-deficient mice is not known, but Klotho mediates calcium-regulated parathyroid hormone secretion (Imura et al., 2007), stimulates FGF signaling in the kidney (Urakawa et al., 2006), and dampens WNT signaling (Liu et al., 2007); the unopposed WNT signaling in Klotho-deficient mice is associated with the premature senescence of progenitor cells in several tissues.

A short retreat from the senescence-centric view of aging. Although these mouse models and other findings indicate a strong association between aging phenotypes and pathologies and cellular senescence, other processes undoubtedly also contribute to aging and age-related disease. One such process is cell death. For example, in one of the mouse models of constitutive p53 activity, there was also excessive p53-dependent apoptosis, which was also proposed to contribute to the progeroid phenotypes shown by these mice (Tyner et al., 2002). In addition, some cells in aging organisms simply lose functionality, which certainly also contributes aging phenotypes. Neurons, for example, lose the ability to form synapses, despite cell bodies remaining viable, which is an important component of many neurodegenerative pathologies (Esiri, 2007). Likewise, cardiomyocytes lose synchronicity of gene expression, which almost certainly affects heart function (Bahar et al., 2006).

How might senescent cells promote age-related pathologies? There are three possible scenarios by which senescent cells might drive aging.

First, as suggested by at least one of the defects shown by Klotho-deficient mice (Liu et al., 2007), cellular senescence can deplete tissues of stem or progenitor cells. This depletion will compromise tissue repair, regeneration, and normal turnover, leading to functional decrements (Drummond-Barbosa, 2008).

Second, the factors that senescent cells secrete affect vital processes–cell growth and migration, tissue architecture, blood vessel formation, and differentiation–and so are tightly regulated. The inappropriate presence of these factors can disrupt tissue structure and function. For example, the MMP3 secreted by senescent fibroblasts inhibits the morphological and functional differentiation of breast epithelial cells (Parrinello et al., 2005) and can promote tumor growth (Liu and Hornsby, 2007).

Third, the SASP includes several potent inflammatory cytokines (Freund et al., 2010). Low-level, chronic, “sterile” inflammation is a hallmark of aging that initiates or promotes most, if not all, major age-related diseases (Franceschini et al., 2007; Chung et al., 2009). Chronic inflammation can destroy cells and tissues because some immune cells produce strong oxidants. Also, immune cells secrete factors that further alter and remodel the tissue environment, which can cause cell/tissue dysfunction and impair stem cell niches. Inflammatory oxidative damage can also initiate carcinogenesis, and the inflammatory milieu can promote cancer by suppressing immune surveillance and/or stimulating malignant phenotypes (Allavena et al., 2008; Grivennikov et al., 2010). Thus, senescent cells might fuel cancer and other age-related pathologies by the same mechanism (the SASP; Fig. 2).

Cause or effect? Evidence that senescent cells drive aging remains circumstantial. The classical approach to
demonstrating cause and effect in biology—eliminate a gene or process, and determine the phenotype—cannot be applied in this case. Organisms in which cells fail to undergo senescence do not live longer; rather, they die prematurely of cancer (Rodier et al., 2007). Another approach might be to engineer mice in which senescent cells can be eliminated as they are formed. Although this feat has not yet been accomplished, recent short-term manipulations in mice revealed another surprising aspect of the senescence response: a role in tissue repair.

**Cellular senescence and tissue repair**

From even a cursory perusal of factors that comprise the SASP, it is obvious that many are important for tissue repair: growth factors and proteases that participate in wound healing, attractants for immune cells that kill pathogens, and proteins that mobilize stem or progenitor cells. Thus, the SASP may serve to communicate cellular damage/dysfunction to the surrounding tissue and stimulate repair, if needed. Two recent studies support this idea.

Upon acute liver injury in mice, hepatic stellate cells initially proliferate and secrete ECM components, which produce a fibrotic scar that eventually resolves. Shortly after the proliferative stage, stellate cells in the injured liver undergo senescence (Krizhanovskiy et al., 2008). This senescence response is accompanied by a decline in ECM production and, as expected from the SASP, increased secretion of several MMPs, which are known to degrade ECM proteins. This finding suggested that the senescence response helps resolve the fibrotic scar. Consistent with this idea, when stellate cells are compromised for their ability to undergo senescence (because of deficiencies in p53 or p16INK4a and p19ARF), mice developed severe fibrosis after acute liver injury.

Similarly, in a mouse model of cutaneous wound healing, the ECM protein CCN1 is highly expressed and important for cell migration, differentiation, and survival. Surprisingly, healing wounds accumulated senescent fibroblasts and myofibroblasts; this did not occur in mice in which wild-type CCN1 alleles were exchanged for mutant alleles encoding CCN1 proteins that cannot bind fibroblasts (Jun and Lau, 2010). Wounds in the mutant mice were excessively fibrotic, but the fibrosis was reversed upon topical application of wild-type CCN1 protein; topical CCN1 induced cellular senescence and the expected expression of MMPs, which presumably helped resolve the fibrosis in the wound.

Together, these studies suggest that cellular senescence, although undoubtedly an important tumor suppressive response, is not simply a failsafe mechanism that is redundant to apoptosis. Rather, the senescence response may also be necessary for resolving normal tissue damage (Fig. 2). This new senescence-associated function in tissue repair suggests that the growth arrest was selected during evolution to suppress tumorigenesis, and possibly excessive cell proliferation or matrix deposition during wound repair. In contrast, the SASP most likely was selected to allow damaged cells to interact with the tissue microenvironment. In addition, some SASP components may have been selected to reinforce the senescence growth arrest.

**Four faces of cellular senescence**

So, how does cellular senescence participate in four complex processes (tumor suppression, tumor promotion, aging, and tissue repair), some of which have apparently opposing effects? We envision the senescence phenotype progressing through temporally regulated steps that orchestrate its activities (Fig. 3).

In cultured cells synchronously induced to senesce by ionizing radiation, the senescent growth arrest establishes rapidly, generally within 24–48 h (DiLeonardo et al., 1994; Rodier et al., 2009, 2011). Cells given a nonsenesce-inducing ionizing
radiation dose recover after 24 h, but those given a senescence dose do not. Thus, there must be a decision period during which oncogenically stressed cells “decide” to senesce. This decision, of course, precludes that cell from developing into a cancer (Fig. 3).

Among the earliest events after the growth arrest, at least in culture, is expression of IL-1α (Orjalo et al., 2009). This cell surface–bound cytokine activates the transcription factors nuclear factor κB (NF-κB) and C/EBPβ (Orjalo et al., 2009), which are required for the expression of many SASP proteins (Fig. 3; Acosta et al., 2008; Kullman et al., 2008; Freund et al., 2010). Some of these second-wave SASP proteins reinforce the growth arrest, whereas others facilitate tissue repair and drive cancer progression (Fig. 3).

We imagine these activities antecede the expression of proteins that permit the immune system to clear senescent cells (Fig. 3). Senescent cells express surface-bound ligands and adhesion molecules that target them for attack by natural killer and other immune cells (Krizhanovsky et al., 2008), although it is not known when these proteins are expressed relative to the SASP. Because senescent cells increase with age, either clear- ance is incomplete (and so senescent cells gradually accumulate) or aged individuals generate senescent cells faster than their immune system can handle, or both (Fig. 3).

Finally, in culture, senescent cells eventually express two microRNAs, mir-146a and mir-146b (Bhaumik et al., 2009), which comprise a negative feedback loop to dampen NF-κB activity (Taganov et al., 2006; Freund et al., 2010). Mir-146a/b increase many days after IL-6 and IL-8 are maximally secreted (Fig. 3), and only in cells that secrete very high levels (Bhaumik et al., 2009). Thus, these microRNAs are an example of another layer of complexity in the regulation of long-term senescence phenotypes, one that “tunes down” the SASP should it reach very high levels (Fig. 3). The induction of these miRNAs may prevent the SASP from generating persistent acute (robust) inflammation, which, unlike low-level chronic inflammation, is designed to be self-limiting (Taganov et al., 2006). Despite their induction, however, the inflammatory response can persist, albeit at a low chronic level, and we speculate that it can drive the chronic pathologies associated with aging.

From cell culture phenomenon to orchestrator of tumor suppression, cancer, wound healing, and aging, cellular senescence has a rich history, marked by unexpected complexity. Some aspects of its physiological significance remain conjecture, and several aspects of its regulation remain enigmatic. As biologists further unravel the foundations and consequences of cellular senescence, they will likely reveal a deepening complexity and additional surprises.

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