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## Senescent Cells and Their Secretory Phenotype as Targets for Cancer Therapy

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### Abstract

Cancer is a devastating disease that increases exponentially with age. Cancer arises from cells that proliferate in an unregulated manner, an attribute that is countered by cellular senescence. Cellular senescence is a potent tumor-suppressive process that halts the proliferation, essentially irreversibly, of cells at risk for malignant transformation. A number of anti-cancer drugs have emerged that induce tumor cells to undergo cellular senescence. However, although a senescence response can halt the proliferation of cancer cells, the presence of senescent cells in tissues has been associated with age-related diseases, including, ironically, late-life cancer. Thus, anti-cancer therapies that can induce senescence might also drive aging phenotypes and age-related pathology. The deleterious effects of senescent cells most likely derive from their senescence-associated secretory phenotype or SASP. The SASP entails the secretion of numerous inflammatory cytokines, growth factors and proteases that can render the tissue microenvironment favorable for tumor growth. Here, we discuss the beneficial and detrimental effects of inducing cellular senescence, and propose strategies for targeting senescent cells as a means to fight cancer.

### Cancer and Aging

Cancer is the second most common cause of mortality in the USA, according to a 2007 report [1]. Nonetheless, cancer death rates have declined by more than 1% per year in men and women over the past 10 years, most likely due to advances in biomedical research; still, more than 1.6 million new cancer cases and half a million deaths from cancer are projected to occur in the USA in 2012 [2]. It is notable that the yearly decline in the cancer death rate is most prominent in younger, compared to older (>45 years of age), individuals [3].

Age is the single most significant risk factor for developing cancer, and the vast majority of malignant tumors that are treated in clinics today occur in older patients [4, 5]. Moreover, age is an important variable that promotes a pro-carcinogenic tissue environment [6]. Hence, in order to develop effective preventive and therapeutic strategies against cancer, it is crucial that we understand the relationship between aging and cancer.

## Cellular Senescence during Aging

Normal human cells have a limited capacity to divide in culture [7]. This essentially irreversible loss of ability to proliferate, even in the presence of growth stimuli, is termed cellular senescence. Cellular senescence has been observed during the aging of several tissues [8, 9]. Senescent cells are linked to several age-associated tissue pathologies, such as osteoarthritis and cardiovascular diseases [10, 11]. Mutations and polymorphisms in senescence-associated genes, such as the cyclin-dependent kinase inhibitor 2A (CDKN2A) gene (p16<sup>INK4a</sup> and p14/p19<sup>ARF</sup>), are implicated in age-related diseases such as coronary heart disease and type 2 diabetes [12–14]. Moreover, the induction of cellular senescence by accelerating telomere shortening in mice can modulate several aspects of aging in numerous tissues and the intact organism [15]. Recently, the elimination of senescent (p16-positive) cells in a premature aging mouse model was shown to delay the progression of certain age-related phenotypes and pathologies [16].

Numerous stimuli can induce cellular senescence. These stimuli include telomere shortening [17], oncogene activation [18], DNA damage [19], activation of tumor suppressor pathways [20], oxidative stress [21, 22], and disrupted chromatin organization [23]. An accumulation of insults resulting from one or more of these stimuli during aging is thought to play a role in the etiology of age-associated degenerative and hyperplastic diseases. Identifying the signaling pathways involved in triggering cellular senescence and understanding the consequences of the accumulation of senescent cells during aging may help design therapeutic strategies to mitigate age-related pathophysiology, including age-related cancer.

## Cellular Senescence and Tumor Suppression

Cellular senescence is recognized as a potent tumor-suppressive mechanism [24]. The induction of cellular senescence prevents the proliferation of potential tumor cells (cells at risk for malignant transformation) by both cell autonomous and non-cell autonomous mechanisms. The presence of senescent cells in premalignant lesions in various mouse tumor models and human patients [25, 26] is consistent with cellular senescence acting as a brake to the development of cancer. Indeed, tumor cells must bypass the mechanisms that impose cellular senescence response in order to proliferate.

### Cell Autonomous Tumor Suppression

The induction and maintenance of the senescence growth arrest depend on the functions of both the Arf/p53/p21 and p16/pRb tumor suppressor pathways [26]. Upregulation of either one or both of these pathways causes an essentially permanent senescence growth arrest. These tumor suppressor pathways inhibit the expression and/or function of genes that promote cell cycle progression. Mutation or epigenetic silencing of at least one crucial regulator of these tumor suppressor pathways allows cancer cells to bypass the senescence checkpoint and progress towards tumorigenesis [18].

### Non-Cell Autonomous Tumor Suppression

In addition to the permanent cell cycle arrest, senescent cells show distinct changes in gene expression [27], including microRNA expression [28], and extracellular matrix composition

[29]. These changes are distinct from those that typically occur during quiescence or terminal differentiation. Cellular senescence entails a robust increase in the expression and secretion of numerous cytokines, chemokines, growth factors and proteases, which are collectively referred to as the senescence-associated secretory phenotype (SASP) or senescence messaging secretome (SMS) [30, 31].

SASP components can potentially attract and activate immune cells, which can remove nearby senescent, damaged and/or potentially tumorigenic cells [32]. Senescent cells can recruit natural killer (NK) cells and T cells to the tissue microenvironment. These immune cells can initiate cytolytic responses on senescent cells and neighboring tumor cells [33, 34]. These immune responses are important in vivo, as a recent report showed that the inactivation of NK cells by antibodies can block senescence-mediated tumor regression in a mouse model [34]. Moreover, the secretion of chemokines and cytokines by senescent cells in premalignant lesions can activate an immune-dependent clearance, termed 'senescence surveillance', by a CD4+ T-cell-mediated adaptive immune response [35].

Other SASP factors have been shown to reinforce the senescence growth arrest in an autocrine manner. These factors include the chemokine (C-X-C motif) receptor 2 (CXCR2) (also called interleukin-8 receptor 2 [IL8R2]), the protease inhibitor plasminogen activator inhibitor-1 (PAI-1), and the pleiotropic protein insulin-like growth factor binding protein-7 (IGFBP-7) [36–38].

## Cellular Senescence and Tumor Promotion and Progression

Tissue microenvironments can provide a milieu that is permissive for malignant tumorigenesis [39]. Such environments are generally characterized by a sustainable supply of growth factors and a mechanism for escaping the immune system and will favor the persistence and growth of cancer cells. Interestingly, senescent cells, by virtue of the SASP, can enhance the proliferation of neoplastic epithelial cells [40]. The SASP can also promote an epithelial-to-mesenchyme transition (EMT) phenotype [41], which is a critical step in the development of metastatic cancer [42]. Further, SASP factors have been shown to promote malignant phenotypes in culture [40, 43] and tumor growth in vivo [44]. For example, senescent cells can stimulate growth and invasiveness of nearby premalignant cells in mouse xenograft models due in part to the secretion of matrix metalloproteinases by the senescent cells [45]. Hence, in ironic contrast to its tumor-suppressive action, SASP factors can also act as potent tumor promoters and thus fuel malignant tumorigenesis.

### Tumor Cell Proliferation

Several SASP factors, such as GRO $\alpha$ , IL-6 and Wnts, can be potent stimulators of cell proliferation [44, 46]. The robust secretion of these growth factors by senescent cells can stimulate and sustain the proliferation of nearby premalignant or malignant cells. Sustained tumor growth can, in turn, eventually overwhelm the host's ability to eliminate cancer cells, tipping the balance in favor of tumorigenic progression. The accumulation of senescent cells with age could potentially serve as a significant source of sustaining growth factors for tumor cells. Hence, the increased risk of incurring cancer with age could in part be a consequence of the increased number of SASP-expressing senescent cells during aging.

However, despite increasing circumstantial and supporting evidence, the impact of senescent cells that accumulate naturally during aging has not yet been rigorously shown to promote late-life cancer progression *in vivo*.

### **Immunosenescence and Immunoediting**

A deficient or subverted immune system has also been shown to play an important role in promoting cancer [47]. While immunosurveillance eliminates damaged and tumor cells, the decreased production of immune cells during aging (immunosenescence) can reduce the ability of the body to remove tumorigenic cells, thereby promoting the development of malignant tumors. In addition to immunosenescence, the ability of tumor cells to eventually adapt to and potentially escape immunosurveillance can further favor the persistence of cancer cells. This process, often termed immunoediting, is observed in tumor cells that are continually exposed to immune cells [48, 49]. Tumor cells isolated from immunocompetent (wild-type) mice, but not tumor cells isolated from immunodeficient (e.g. *RAG2<sup>-/-</sup>*) mice, were able to develop tumors when retransplanted into naive immunocompetent hosts [50]. This result suggests that tumors formed in the absence of an intact immune system are more immunogenic than tumors that arise in immunocompetent hosts. In the case of tumors that develop in immunodeficient environments, tumor cells are no longer recognized by the immune system as foreign. The presence of SASP-expressing senescent cells around tumors can potentially exacerbate tumor immunoediting and eventually permit the growth of immune-resistant cancer cells.

### **Cellular Senescence and Cancer Therapy**

Therapies for patients with advanced cancer generally include surgical tumor resection, intensive multimodal chemotherapy, radiation therapy, or a combination of these regimens. Because the tumor-suppressive senescence growth arrest is so potent and essentially irreversible, regimens that induce tumor cells to senesce have been proposed as potential anti-cancer therapies [51]. This pro-senescence therapy approach has been developed and refined over the past few years, and currently a number of compounds with senescence-inducing activities are in clinical trials. However, the induction of cellular senescence as an anti-cancer therapy strategy is complicated by the potential pro-tumorigenic properties of senescent cells and the SASP. Thus, the ability to harness the anti-tumor activity of the senescence growth arrest must be balanced against the tumor-promoting potential of the SASP.

### **Senescence-Induction Therapy**

Several of the widely used cancer treatments, such as certain chemotherapeutic agents, can promote cellular senescence both in culture and *in vivo*. Aside from their cytotoxic actions in some tumor cells, certain anti-cancer drugs, as well as ionizing radiation, can trigger cellular senescence primarily by inducing severe DNA damage [17]. The ability of these agents to promote cellular senescence could play a role in inhibiting tumor growth. Indeed, the induction of senescence in response to chemotherapy predicted a better outcome in human patients with advanced colon cancer [52]. Although many tumor cells have acquired mutations that allow them to bypass cellular senescence, reintroducing factors that can

reactivate senescence pathways has the potential to repress cancer cell growth. Such factors, whether they be biological or chemical molecules that induce and/or maintain the senescence growth arrest, remain promising as therapies against cancer, providing the potentially deleterious SASP can be blunted or ablated.

PTEN, a key mediator of the AKT/PKB pathway, is one of the most commonly lost tumor suppressor genes in human tumors, particularly in prostate cancer [53]. Loss of one copy of the PTEN gene strongly predisposes to cancer development [54], while complete PTEN loss can lead to a p53-dependent cellular senescence response [55]. For this reason, human prostate cancer does not select for complete PTEN loss, highlighting the importance of PTEN haploinsufficiency for cancer initiation and progression [56]. Therapeutic interventions that severely compromise PTEN activity or the AKT/PKB pathway can be an effective strategy to induce senescence in vivo. Importantly, PTEN-induced cellular senescence does not trigger a DNA damage response or hyperproliferative stage [57], which is typically induced by the activation of many oncogenes, and thus avoids an accumulation of damaged cells that can favor cancer progression.

Preclinical trials of pharmacological agents that activate the senescence-inducing p53/p21 pathway in cancer cells have been initiated [58]. LY83583 (6-anilino-5,8-quinolinequinone), a pharmacological inducer of p21, can promote cellular senescence and inhibit tumor cell proliferation in cultured colorectal cancer cells [59]. Small molecules, such as PRIMA-1 and MIRA-1, which can restore the function of mutated p53, can also promote tumor regression [60, 61]. PRIMA-1<sup>MET</sup> (Aprea AB) is currently in phase II clinical trials for the treatment of refractory hematological malignancies and prostate cancer. Enhancing stability and/or activity of wild-type p53 by disrupting p53/Mdm2(Hdm2) interaction has also been developed as a promising anti-cancer therapy [51, 62]. Serdemetan (JNJ-26854165), an Mdm2 inhibitor, is currently in phase I clinical trials (Johnson & Johnson Pharmaceutical Research & Development) for the treatment of advanced stage or refractory solid tumors. RO5045337, another Mdm2 inhibitor, is also in phase I clinical trial (Hoffmann-La Roche) for the treatment of hematologic neoplasms. Finally, a gene therapy approach for reintroducing p53 to fight cancer has been used in China since 2003. Gendicine<sup>TM</sup> (Shenzhen SiBiono GeneTech), an adenovirus-based vector for expressing recombinant human p53, is used as a treatment for head and neck squamous cell carcinoma.

Tumor cells are thought to be dependent on one or more specific oncogenes in order to maintain their malignant phenotypes [63]. The inactivation of a single oncoprotein (e.g. Myc) in experimental mouse tumors can induce tumor cell senescence and eventual regression of the tumors [64]. Small molecules that downregulate Myc expression or target interactions between Myc and its obligatory partners (e.g. Max) are being developed as anti-cancer therapies [65]. Quarfloxin (CX-3453), which inhibits Myc expression [66], is in phase II clinical trials (Cylene Pharmaceuticals) to treat low to intermediate grade neuroendocrine carcinomas.

### Anti-SASP Therapy

While the induction of tumor cell senescence can halt tumor growth, the accompanying SASP can eventually promote the proliferation and/or invasion of neighboring cancer cells

that escape the senescence therapy and/or the immune system, resulting in cancer relapse (fig. 1a). It would therefore be highly desirable to develop strategies aimed at inhibiting the cancer-promoting components of the SASP (fig. 1b). Drugs that specifically target the SASP have not yet been developed, certainly not for clinical use, but several strategies for the development of such drugs can be envisioned.

The SASP occurs as a delayed response to DNA damage [67, 68]. An important initiation event in development of the SASP is increased expression of the plasma membrane-bound form of the cytokine IL-1 $\alpha$ , which, through a juxtacrine mechanism, activates signaling through the plasma membrane bound IL-1 receptor [69]. Thus, compounds that interrupt IL-1 receptor signaling may hold promise for preventing or suppressing the SASP.

The SASP also depends upon activation of other intracellular signaling pathways, such as the p38MAPK (p38 mitogen-activated protein kinase)/NF- $\kappa$ B (nuclear factor- $\kappa$ B) pathway [30, 70, 71]. Inhibition of p38MAPK is a potent repressor of the SASP, suggesting that small molecule p38MAPK inhibitors might be effective SASP suppressors in vivo [71]. Recently, as a result of a small molecule screen for SASP inhibitors, glucocorticoids (corticosterone and cortisol) were shown to inhibit the expression and secretion of several SASP factors [72]. Glucocorticoids, which are already used clinically to treat a variety of inflammatory diseases [73], may therefore be beneficial for restraining the cancer-promoting effects of the SASP.

### **Alternative Senescence-Based Therapy**

While a SASP is observed in a variety of senescent cells in culture (fibroblasts, epithelial cells, endothelial cells, etc.) and in vivo in both mice and humans, not all senescent cells express the SASP [30, 74]. Cells that undergo senescence in response to oncogene activation, replicative exhaustion, and agents that damage DNA or disrupt the epigenome all develop a SASP. In contrast, cells that senesce owing to overexpression of the p16<sup>INK4a</sup> or p21 cell cycle inhibitors do not express the SASP [20]. One novel and potentially promising anti-cancer strategy, then, would be to develop biological or small chemical molecules that specifically upregulate p16 and p21 levels in cancer cells to induce a senescence growth arrest without inducing a SASP (fig. 1c).

### **Senescence-Elimination Therapy**

While inhibition of the SASP following therapies that induce cellular senescence can be a potential strategy to fight cancer, the accumulation of senescent cells in aging tissues may fuel the development of late life cancer in the absence of any pro-senescence anti-cancer therapies [16]. It may therefore be beneficial to develop strategies for eliminating senescent cells, either through the immune system or through biological or chemical interventions.

Senescent cells via their SASP have been shown to attract and activate immune cells to stimulate their own clearance [33, 34]. Senescent cells express ligands for cytotoxic immune cells such as NK cells, and thus can be specifically eliminated by the immune system [33]. The accumulation of senescent cells with age raises the possibility that the aging milieu may be permissive for the retention of senescent cells. Because the immune system declines in function during aging [75], the aging immune system may also become less capable of

clearing senescent cells. Thus, therapies that boost the immune system in older patients may help eliminate senescent cells (fig. 1d). The creation of antibodies that specifically recognize and trigger the elimination of senescent cells would be ideal, however such antibodies have not yet been developed.

Finally, the recent creation of a transgenic mouse model that allows the elimination of senescent cells provides proof-of-principle that the clearance of senescent cell can ameliorate the development of certain age-associated pathologies [16]. Although the effects of senescent cell clearance on the development of cancer is not yet known, this idea is now ripe for testing.

## Conclusions

Aside from their cytotoxic actions, several cancer therapies that are currently in use or being tested clinically can also induce cellular senescence. While these types of therapies may prove successful in reducing tumor growth and progression, the SASP produced by senescent cells may increase the risk of cancer relapse. It is therefore important to follow the consequences of these therapies on cancer recurrence. Inhibiting the SASP following induction of tumor cell senescence may be necessary to prevent cancer relapse. It may also be critical to develop pharmacological agents that can induce the senescence of tumor cells without triggering a SASP. In conclusion, whatever the choice of the cancer treatment, it is essential to take into consideration whether or not senescent cells are being produced, and, most importantly, whether or not these senescent cells express a SASP.

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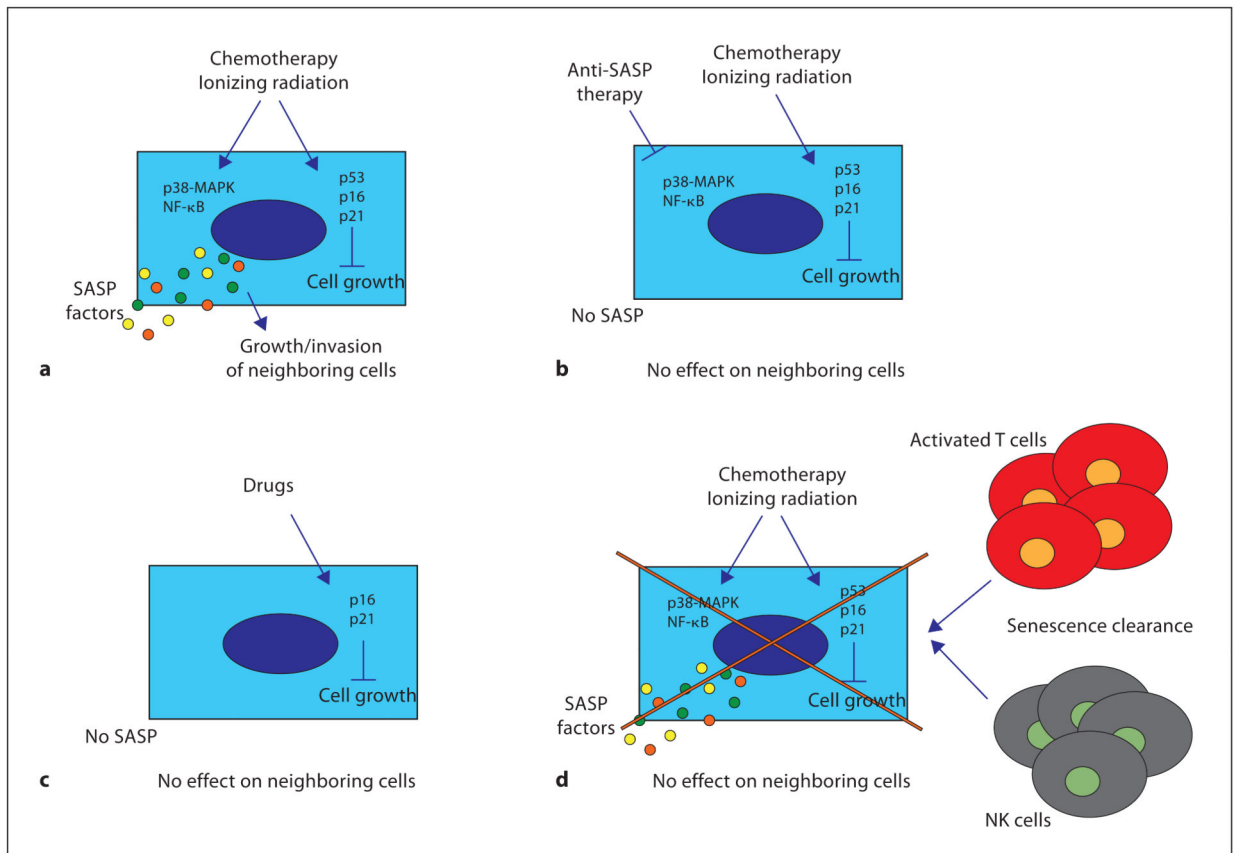
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**Fig. 1.**

Strategies to target cellular senescence for cancer therapy. **a** Cellular senescence can modulate tumor growth via cell autonomous and non-cell autonomous mechanisms. Senescent cells can express a SASP, components of which can stimulate the proliferation and/or invasiveness of neighboring tumor cells. **b** Inhibition of the SASP, or SASP components, produced by senescent cells can limit the detrimental effects of cancer therapies that induce a senescence growth arrest accompanied by a SASP. **c** Small molecules that specifically upregulate p16 and p21, without inducing DNA damage, can trigger senescence in tumors without an accompanying SASP. **d** Immunotherapy that increases immunosurveillance may help eliminate senescent cells and consequently their impact on the proliferation and/or invasion of nearby premalignant or malignant cells.