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The Potent and Paradoxical Biology of Cellular Senescence in Cancer

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senescence, SASP, immune surveillance, therapy-induced senescence, one-two punch therapy, senolytic

Abstract

Cellular senescence is a tumor-suppressive program that promotes tissue homeostasis by identifying damaged cells for immune-mediated clearance. Thus, the ability to evade senescence and the ensuing immune surveillance is a hallmark of cancer. Reactivation of senescence programs can result in profound immune-mediated tumor regressions or sensitize tumors to immunotherapy, although the aberrant persistence of senescent cells can promote tissue decline and contribute to the side effects of some cancer therapies. In this review, we first briefly describe the discovery of senescence as a tumor-suppressive program. Next, we highlight the dueling good and bad effects of the senescence-associated secretory program (SASP) in cancer, including SASP-dependent immune effects. We then summarize the beneficial and deleterious effects of senescence induction by cancer therapies and strategies in development to leverage senescence therapeutically. Finally, we highlight challenges and unmet needs in understanding senescence in cancer and developing senescence-modulating therapies.

INTRODUCTION

Senescence: stress response program characterized by stable cell cycle arrest coupled with a secretory program that modulates the tissue microenvironment

Senescence-associated secretory phenotype (SASP): a secretory program that is a hallmark of senescent cells and modulates the tissue microenvironment

Oncogene-induced senescence (OIS): premature or nonreplicative senescence resulting from strong mitogenic signals triggered by oncogene activation

Cellular senescence is a physiological and pathological stress response program that has beneficial and detrimental effects on human health and plays a particularly important role in cancer. Senescence provides a barrier to tumorigenesis, and indeed, genes that promote senescence are frequently inactivated in malignant tumors. The senescence program involves coordination of cell cycle arrest and the secretion of factors, known as the senescence-associated secretory phenotype (SASP), that modulate the tissue environment. The SASP stimulates tissue remodeling and modulates immune responses, leading to the clearance of senescent cells in some settings and their persistence in others. The therapeutic potential of inducing senescence in tumors has been established in both preclinical and clinical studies showing that the antitumor activities of many cancer therapies result to some degree from their ability to reengage the senescence program. By contrast, the accumulation of senescent cells in tissues can produce chronic inflammation and tissue dysfunction and, in some settings, can promote tumor progression or contribute to the side effects of cancer therapy. As such, therapies that promote or enhance senescent cell clearance provide a new, immune-modulating approach to cancer treatment and may also be relevant to the management of a wide range of other human pathologies.

DISCOVERY OF SENESCENCE

Cellular senescence was originally described by Hayflick & Moorhead (1961) as resulting from the finite proliferative capacity of cultured human fibroblasts. Hayflick postulated that cellular senescence regulates normal tissue homeostasis and is an active barrier to tumorigenesis. The first hint at the underlying molecular mechanism came in the late 1980s when Wright et al. (1989) discovered that DNA tumor viruses could extend the cultured lifespan of normal human fibroblasts. Tumor virus proteins such as SV40 T antigen bind to and inhibit the activity of p53 and retinoblastoma protein (pRb) to bypass M1 phase or G1/S interface cell cycle arrest. Viral infection thus allows fibroblasts to bypass senescence (i.e., M1) and continue dividing until M2 crisis, which is characterized by telomere fusions, chromosomal breakage-fusion cycles, and, ultimately, cell death. If at any time after M1 bypass the T antigen is removed, the cells stop dividing and become senescent (Shay et al. 1992). Other researchers went on to demonstrate that the p53/pRb program activation results from telomere attrition and that genetic activation of telomerase allows cancer cells to avert replicative senescence (Huang et al. 2013, Morin 1989, Vinagre et al. 2013). Together these works invigorated interest in senescence biology, specifically in the context of cancer.

Validation of senescence as a tumor-suppressive program came in the late 1990s when Serrano, Lowe, and colleagues described nonreplicative or so-called premature senescence induced by oncogene activation (Serrano et al. 1997). Oncogene-induced senescence (OIS) explained the long known but poorly understood basis for oncogene cooperation in the transformation of primary cells (i.e., senescence bypass). Oncogenic RAS expression triggers altered DNA replication, which ultimately engages DNA damage repair (DDR) programs and accumulation of p53, p21, and p16, resulting in cell cycle arrest and senescence induction (Bartkova et al. 2006, Di Micco et al. 2006, Halazonetis et al. 2008, Serrano et al. 1997). Activation of DDR programs by replication stress in response to strong mitogenic signals is thought to be required for OIS (Bartkova et al. 2006, Campisi & d'Adda di Fagagna 2007, Di Micco et al. 2006, Halazonetis et al. 2008). Subsequent work characterized OIS in premalignant, but not malignant, tumors and confirmed that OIS limits tumor development in mice (Braig et al. 2005, Chen et al. 2005, Collado et al. 2005). Because various forms of cellular injury can induce premature senescence, it is now widely accepted that premature senescence is a general response to limit cancer development (Coppe et al. 2010).

IMPACT OF SENESCENCE: GOOD VERSUS EVIL

Iatrogenic morbidity: therapy-induced side effects resulting from the treatment itself

To understand senescence in cancer, it is important to appreciate the paradox between the physiological role senescence plays in development and tissue repair and the pathological role senescence plays in age-related diseases such as osteoarthritis; osteoporosis; pulmonary, renal, and liver fibrosis; pulmonary hypertension; Alzheimer's disease and other neurological disorders; atherosclerosis and other vascular and heart diseases; and even metabolic diseases including diabetes, obesity, and cancer (Paramos-de-Carvalho et al. 2021). Senescent cells accumulate over the lifespan of humans, nonhuman primates, and rodents in several organs such as the skin, heart, lung, liver, spleen, kidney, and brain (Paramos-de-Carvalho et al. 2021). In addition to leading to tissue decline, this phenomenon may also increase cancer risk, and indeed, studies suggest that the chronic inflammation produced from senescent cells can promote tumor initiation or progression (Lex et al. 2020). In addition, while senescence induction by common cancer therapies, including cytotoxic chemotherapy and radiation, can have antitumor effects, these therapies simultaneously increase organismal senescence burden and contribute to premature aging, iatrogenic morbidity, and even therapy-induced secondary malignancies (Goy et al. 2022, Marcoux et al. 2013, Ness et al. 2015). Thus, senescence has dueling tumor-suppressive and procancer effects (Rodier & Campisi 2011).

SENESCENCE MECHANISMS

The hallmarks of cellular senescence include (*a*) stable, if not irreversible, cell cycle arrest; (*b*) marked alterations in high-order chromatin organization and dramatic changes in gene expression; (*c*) distinctive morphological features (e.g., multiple or enlarged nuclei, flattened cytoplasm); (*d*) enhanced lysosomal activity as revealed by pH-dependent senescence-associated β-galactosidase (SA-β-gal) staining; (*e*) impaired nuclear integrity (LaminB1 loss); (*f*) metabolic reprogramming; (*g*) mitogenic insensitivity; (*h*) apoptotic resistance; and (*i*) activation of the tissue-remodeling SASP (**Figure 1**) (Hernandez-Segura et al. 2018). Despite these generalities, the markers used to diagnose senescent cells are not strictly unique to senescent states, and emerging evidence indicates that there may be vast heterogeneity in senescence programs that further confound their identification in vivo (Gorgoulis et al. 2019). To this end, the National Institutes of Health (NIH) Common Fund established the SenNet (Cellular Senescence Network) Program (**https://commonfund.nih.gov/senescence**) to comprehensively identify and characterize the molecular features of senescence in various states of human health and across organism lifespan.

What is clear is that senescence induction requires a widespread chromatin remodeling program that involves the repression of proliferative genes and the activation of genes that modulate the tissue environment. Genetic models have demonstrated the central importance of p53 and pRb programs in orchestrating cell cycle arrest, although the relative reliance on these pathways varies among cell types (Chicas et al. 2010). In normal cells, this occurs through the p21 and p16 cyclin-dependent kinase inhibitors, which are activated by p53 or pRb, respectively, and indeed both p21 and p16 are broadly used to identify senescent cell states. In turn, these proteins trigger proliferative arrest and pRb-mediated remodeling of chromatin into senescence-associated heterochromatin foci (Narita et al. 2003). Studies using chromatin immunoprecipitation and sequencing and other epigenetic analyses indicate that genes controlled by pRb-E2F accumulate more repressive marks than those that occur in quiescent cells (Chicas et al. 2012, Nijwening et al. 2011).

The above observations help explain why senescence-associated cell cycle arrest is particularly stable. Nonetheless, many anticancer agents can induce senescence-like programs in p53-mutant cancers, and the absence of p53 seems to reduce the durability of cell cycle arrest (Jochems et al. 2021). The p16 program is also deregulated in cancer cells but may not be strictly required for certain forms of therapy-induced senescence (Li et al. 1994, Parry et al. 1995). Improved

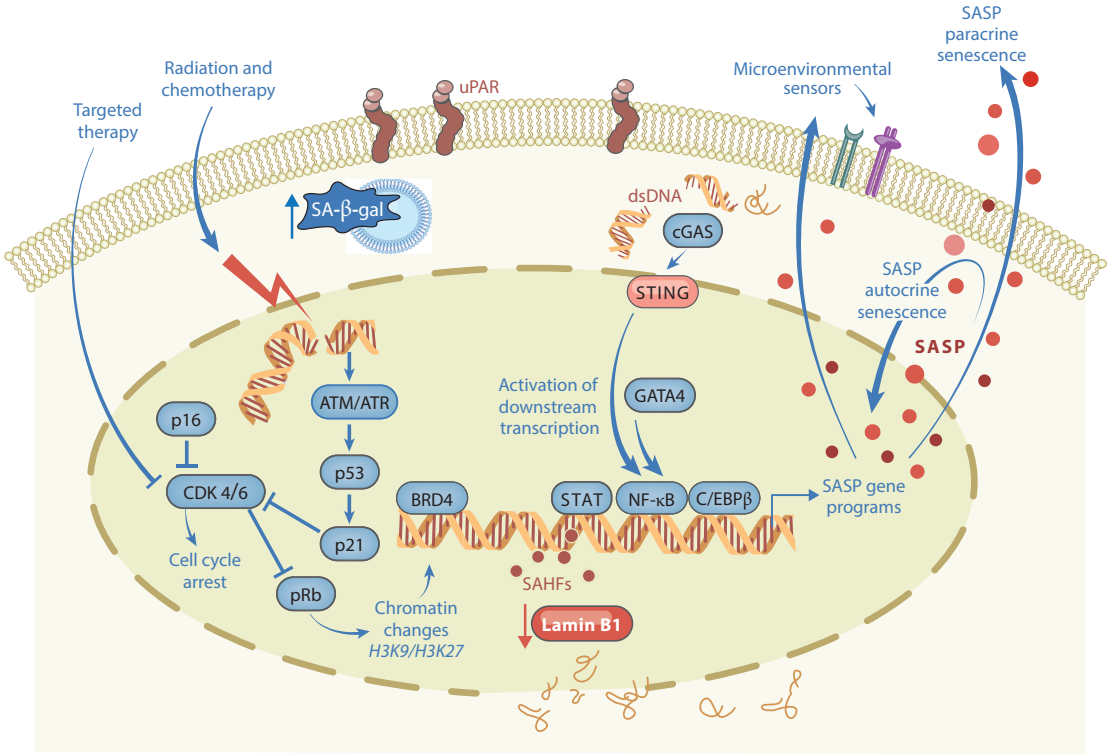

Figure 1

Senescence and SASP mechanisms. Common cancer treatments including chemotherapy, radiation therapy, and targeted therapy induce senescence predominantly by inducing DNA damage or inhibiting cell cycle kinase inhibitors. These actions in turn modulate the p53 and pRb programs to orchestrate cell cycle arrest and epigenetic remodeling to activate the SASP. Loss of nuclear envelope integrity, a hallmark of senescence, may also result in cytoplasmic DNA, sensed by cGAS, to activate STING signaling to induce NF-κB and interferon-associated genes. The SASP stimulates tissue remodeling, recruits immune cells, and alters immune cell states; the SASP may also alter senescent cells' ability to receive environmental signals in a manner that influences their ultimate state and fate. Abbreviations: cGAS, cyclic GMP-AMP synthase; dsDNA, double-stranded DNA; SA-β-gal, senescence-associated β-galactosidase; SAHFs, senescence-associated heterochromatic foci; SASP, senescence-associated secretory phenotype; STING, stimulator of interferon genes; uPAR, urokinase-type plasminogen activator receptor. Figure copyright 2023 Memorial Sloan Kettering Cancer Center. All rights reserved.

understanding of differences in senescence mechanisms in normal and cancer cells may help guide the use of senescence-modulating therapies.

The marked chromatin remodeling that accompanies senescence also induces the SASP, including secreted factors such as immune-modulatory cytokines and chemokines, angiogenic growth factors, and matrix metalloproteinases (MMPs) (Chicas et al. 2010, Krtolica et al. 2001, Lasry & Ben-Neriah 2015, Narita et al. 2003, Tasdemir et al. 2016). Collectively, the SASP stimulates tissue remodeling and immune cell recruitment and alters immune cell states; it may also reinforce the senescent state through autocrine and paracrine effects (Acosta et al. 2008, 2013, Wang et al. 2022). As such, the SASP mediates senescent cell communication with the tissue microenvironment.

The SASP is regulated at the epigenetic, transcriptional, translational, and posttranslational levels and is critically regulated by the transcription factor NF-κB (**Figure 1**) (Chien et al. 2011). NF-κB is activated during senescence through a variety of mechanisms depending on context

(Acosta et al. 2008, Alimonti et al. 2010, Bhaumik et al. 2009, Chien et al. 2011, Freund et al. 2011, Orjalo et al. 2009). One mechanism to initiate and maintain the SASP involves NF-κB activation by cGAS (cyclic GMP-AMP synthase)/STING (stimulator of interferon genes), which may detect cytoplasmic micronuclei arising through loss of nuclear membrane integrity (Dou et al. 2017). The ability of NF-κB and other SASP-promoting transcription factors to access SASP factor–encoding genes requires the reorganization of enhancers, and indeed many such genes acquire large enhancer elements that accumulate the BET domain protein BRD4 (Chien et al. 2011, Tasdemir et al. 2016). Interestingly, BET inhibitors, broadly developed as cancer therapeutics, are extremely potent inhibitors of the SASP.

Beyond transmitting tissue-remodeling signals to the environment, senescence also alters cells' ability to receive environmental signals in a manner that influences their ultimate state and fate. This process involves vast changes to the surface proteome, including increased expression of growth factor and cytokine receptors, cell adhesion molecules, natural killer (NK) cell ligands, and components of MHC class I/HLA (Chen et al. 2022, Marin et al. 2022). One outcome of these changes includes a hypersensitization to the presence of interferon gamma (IFN-γ), which in turn increases antigen-presenting capabilities and makes senescent cells more immunogenic (Chen et al. 2022, Marin et al. 2022). Another may involve increased expression of NK cell ligands to enhance NK cell recognition (Iannello et al. 2013, Sagiv et al. 2016). Cooperation between SASP and tissue-sensing programs likely plays a major role in determining the impact of senescent cells on tissue biology.

THE BIOLOGY OF THE SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE MAY CONTRIBUTE TO THE PARADOXICAL EFFECTS OF SENESCENCE IN CANCER

Because the SASP is the effector arm of the senescence program, leading to either clearance of senescent cells or chronic inflammation, it lies at the center of the dueling good and bad, regenerative and inflammatory, and tumor-suppressive and tumor-promoting effects of senescence (**Figure 2**). Similarly, SASP induction via senescence-inducing therapies can activate immunemodulatory programs that can be beneficial or detrimental depending on the context. Admittedly, the literature is conflicting and at times downright confusing, especially given the plethora of reports that completely ignore the immune effects of the senescence program.

The first hint that senescent cells could stimulate their own clearance came from studies examining the consequences of p53 inactivation in tumor maintenance. Specifically, Xue et al. (2007) showed that p53 reactivation induces senescence in hepatic tumors and activates innate antitumor immune surveillance programs that target and clear senescent tumor cells. Depletion of macrophages, neutrophils, and NK cells delayed tumor regression, suggesting that the therapeutic benefit of senescence reactivation is secondary to immune clearance (Xue et al. 2007).

Later studies confirmed that the immune surveillance of premalignant cells contributes to the tumor-suppressive potential of the senescence program. In the liver, the SASP triggers removal of premalignant hepatocytes by activating an antigen-specific $CD4^+$ T cell-mediated adaptive immune response that co-opts the innate immune system to clear premalignant senescent hepatocytes (Kang et al. 2011). Similarly, in the setting of chronic liver inflammation, SASP signals from senescent hepatic stellate cells induce macrophage M1 polarization to create an antitumor immune microenvironment that can suppress fibrosis, cirrhosis, and liver tumorigenesis (Lujambio et al. 2013).

Many common cancer treatments, such as chemotherapy and radiotherapy, can reengage senescence programs in established tumors, leading to activation of SASP-mediated antitumor

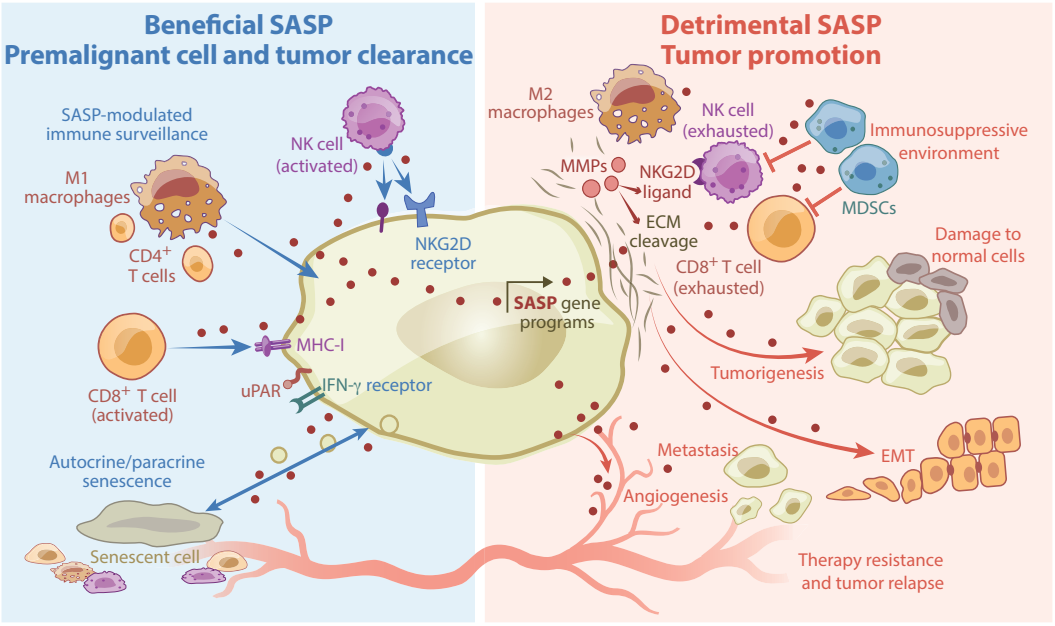

Figure 2

SASP biology may underpin the beneficial and deleterious effects of senescence in cancer. The SASP is the effector arm of the senescence program, lying at the center of the dueling beneficial and detrimental effects of senescence. In established tumors the SASP can stimulate an immune response against the tumor, leading to outright tumor rejection or increased sensitization to immune checkpoint blockade. Conversely, in other contexts the SASP can facilitate tumor growth, invasion, and metastasis and contribute to therapy resistance and treatment side effects. Abbreviations: ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; IFN-γ, interferon gamma; MDSC, myeloid-derived suppressor cell; MHC-I, major histocompatibility complex class I; MMPs, matrix metalloproteinases; NK, natural killer; SASP, senescence-associated secretory phenotype; uPAR, urokinase-type plasminogen activator receptor. Figure copyright 2023 Memorial Sloan Kettering Cancer Center. All rights reserved.

surveillance programs and robust tumor regressions (Chang et al. 1999, Chien et al. 2011, Meng et al. 2012, Roninson 2003, Schmitt et al. 2002, J. Xu et al. 2018). Chien et al. (2011) reported that SASP-mediated NK cell surveillance could be induced by cyclophosphamide in a murine B cell lymphoma model; SASP inhibition eliminated NK cell targeting and reduced survival. Other chemotherapy agents can induce senescence in various experimental models, leading to T cell–mediated tumor regressions or enhanced response to immune checkpoint blockade (Hao et al. 2021, Paffenholz et al. 2022). Senescence and the SASP may also contribute to the efficacy of radiation therapy and may explain in part why radiation is more effective in immune-competent than immune-deficient models (Meng et al. 2012, J. Xu et al. 2018). While the impact of senescence induction on treatment outcomes in human patients has not been studied in detail, senescent cells are observed in patients after radiation and chemotherapy, and senescence inducers can synergize with immune checkpoint blockade (Kusunoki et al. 2010, Roberson et al. 2005, Saleh et al. 2021, te Poele et al. 2002).

Cytostatic therapies: therapies that inhibit cell division but have no cell-killing effect

More recently, targeted agents have also been shown to induce senescence, which in some contexts triggers profound tumor regressions (Chibaya et al. 2022). As an example, MEK inhibition and downstream CDK 4/6 inhibition synergize to induce senescence in *KRAS*-mutant lung cancer cells, leading to SASP-mediated tumor regressions involving NK cells (Ruscetti et al. 2018). Thus, SASP-mediated immune surveillance can induce robust antitumor responses even to cytostatic therapies. Interestingly, the same drug combination also induces senescence

in *KRAS*-mutant pancreas tumor cells, although, in this context, SASP induction leads to microenvironmental remodeling that stimulates T cell recruitment and sensitizes the tumor to immune checkpoint blockade (Ruscetti et al. 2020). Separately, long-term ERK inhibition induces senescence in *KRAS*-mutant pancreas cancer via MYC degradation and p16 reactivation, suggesting senescence induction as a clinically relevant mechanism of action (Hayes et al. 2016). In $BRAF^{V600E}$-mutant melanoma, genetic and pharmacologic inhibition of ERK5 elicits senescence and the SASP, similarly contributing to therapeutic effects (Tubita et al. 2022). Collectively these studies show how targeted therapies that are cytostatic can lead to tumor regressions in vivo if they provoke senescence and a subsequent immune response.

In some settings, induction of senescence and the SASP has the opposite effect, promoting tumor progression and therapy resistance. Some of the first evidence that senescence could promote tumor progression came from a 2001 report that senescent human fibroblasts stimulate premalignant and malignant, but not normal, epithelial cells to form tumors in mice (Krtolica et al. 2001). The tumor-promoting SASP effect appears to be due to proinflammatory SASP factors such as IL-6 and IL-8 that can promote epithelial-to-mesenchymal transition, recruit tumor-promoting macrophages, and inhibit cytotoxic T cell function (Coppe et al. 2008, Eggert et al. 2016, Ruhland et al. 2016). IL-6 secreted by senescent dermal fibroblasts stimulates the expression of the nonclassical MHC molecule HLA-E, which suppresses T and NK cell responses (Pereira et al. 2019). Similarly, SASP-associated MMP activity leads to shedding of NKG2D ligands, which inhibits NK and $CD8^+$ T cell targeting (Salminen 2021). The SASP also contributes to chemotherapy and radiation therapy resistance (Demaria et al. 2017, Nicolas et al. 2022, Samaraweera et al. 2017). Doxorubicin- and radiation-induced senescence, for example, can induce local and systemic inflammation and thereby promote cancer relapse and metastasis (Demaria et al. 2017, Nicolas et al. 2022, Samaraweera et al. 2017). The SASP can trigger a protumorigenic inflammatory milieu that helps senescent cells evade immune clearance.

The SASP can also contribute to the impact of senescent cells on tissue decline. Chemotherapy-induced senescence and SASP in normal tissues likely contributes to chemotherapy-induced peripheral neuropathy, doxorubicin-induced bone marrow suppression and cardiotoxicity, and radiation- and bleomycin-induced pulmonary fibrosis and secondary malignancies (Aoshiba et al. 2003, Calls et al. 2021, Mitry et al. 2020, Peng et al. 2020, Soysouvanh et al. 2020). Emerging reports in childhood, adolescent, and young adult cancer survivors found that chemotherapy increases organismal senescence burden and molecular age and correlates with frailty (Smitherman et al. 2020). In the case of taxane-induced peripheral neuropathy, unexpectedly, molecularly young patients, defined as those of older age but with lower pretreatment senescence burden, were at highest risk (Mitin et al. 2022). Recent evidence suggests that radiation-induced secondary malignancies can arise from senescent cells that evade immune clearance and subsequently reenter the cell cycle (Goy et al. 2022). In a separate study, the SASP was shown to recruit NK cells to target and clear senescent cells in immunocompetent mice, whereas in immune-deficient mice, senescent cells were not cleared, increasing osteosarcoma development following radiation (Kansara et al. 2013). Lack of senescent cell clearance appears to contribute to the detrimental pathological effects of therapy-induced senescence.

In sum, depending on context, SASP induction can be beneficial, contributing to tumor suppression and efficacy of common cancer therapies and sensitizing tumors to immune checkpoint blockade, or it can be detrimental, facilitating tumor growth, invasion, and metastasis and contributing to therapy resistance and iatrogenic morbidity. While its beneficial and detrimental effects are clear, we lack an understanding of the mechanisms that determine the outcomes of senescence in various settings. Such understanding requires molecular characterization of senescent states and development of corresponding biomarkers.

HOW CAN THE PARADOXICAL EFFECTS OF SENESCENCE AND THE SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE BE EXPLAINED?

Heterochronic parabiosis: the surgical pairing of the circulatory system of a young mouse with that of an old mouse

What might underlie the paradoxical effect of the SASP program on cancer phenotypes? While the SASP is initially tumor suppressive, inducing cell cycle arrest and promoting immune surveillance, it is thought to be detrimental in the long term (**Figure 2**) (Wang et al. 2022). Why are some senescent cells cleared whereas others evade immune targeting? Heterogeneity among cancer cells and among tissues represents nonmutually exclusive hypotheses to explain differential SASP responses. Thus, to leverage senescence therapeutically, we must consider context-related factors that may determine whether the SASP, and senescence in general, is tumor suppressive or tumor promoting.

First, SASP programs are heterogeneous, and the composition of SASP factors is influenced by cell type, genetic background, and senescence trigger (Coppe et al. 2008, Rodier et al. 2009). Moreover, the SASP is dynamic and evolves over time, adding yet another layer of contextual complexity (De Cecco et al. 2019). In an effort to assess SASP heterogeneity, the first proteome-based database of SASPs, the SASP Atlas (**http://www.SASPAtlas.com**), was recently published (Basisty et al. 2020) and is expected to be updated continuously.

Second, factors that influence how the environment responds to senescent cells vary among tissues (Ruscetti et al. 2018, 2020). For example, because the lungs are relatively rich in NK cells, the SASP triggers NK cell surveillance in the lung, whereas in the pancreas, it leads to recruitment of $CD8^+$ T cells (Ruscetti et al. 2018, 2020). In addition, as the epigenome of tumor cells can be reprogrammed by the microenvironment, the epigenetic states of tumor cells and of the surrounding tissue may influence the SASP (Guo et al. 2017).

Third, systemic physiologic factors may also influence the effects of senescence on tissue biology. The transfer of a small number of senescent cells was sufficient to decrease physical fitness and accelerate aging in young mice, whereas transplanting even fewer senescent cells was required for similar effects and decreased survival in older mice (M. Xu et al. 2018). These detrimental effects were mitigated by senescent cell clearance (M. Xu et al. 2018). Similarly, heterochronic parabiosis selectively decreases senescence and SASP markers and can reverse aging genetic signatures in aged mice (Rebo et al. 2016, Yousefzadeh et al. 2020). In human patients, organismal senescence burden, defined as p16 expression in peripheral blood mononuclear cells, has been proposed as a marker of physiological age and a predictor of toxicity in patients treated with chemotherapy (Muss et al. 2020).

Finally, immune-mediated factors likely determine the propensity of senescent cells to be eliminated or persist. Immune function changes with age and is severely compromised by many cancer therapeutics. In support of this concept, mice defective in perforin, a mediator of immune cytotoxicity, accumulated more senescent cells with age, which accompanied a progressive state of chronic inflammation, tissue fibrosis, and compromised organ function (Ovadya et al. 2018). Mitochondrial dysfunction-induced defects in systemic T cell functionality were recently shown to increase senescent cell burden, resulting in multimorbidity and premature death (Desdin-Mico et al. 2020). Conversely, depletion of senescent cells in aged mice mitigates the SASP, attenuates age-related deterioration of several organs, and delays tumorigenesis (Baker et al. 2011, 2016).

The heterogeneity of the SASP and other tissue factors complicates our understanding of its role within tissues and our ability to reconcile differing effects across different organisms, microenvironments, and cell types and in response to various stimuli (Basisty et al. 2020, Gorgoulis et al. 2019, Jochems et al. 2021). This heterogeneity, especially regarding factors determining whether senescent cells induce or evade immune clearance, helps explain the apparently conflicting effects

of therapy-induced senescence. Thus, the role of senescence in diverse biological processes must be studied in the contexts of cell lineage, cell genotype, cell epigenome, senescence inducer, tissue microenvironment, and systemic physiological factors.

Senotherapies: drugs that target senescent cells including senolytics and senomorphics

Senolytics: therapies that preferentially or preferably selectively kill senescent cells

Senomorphics: therapies or drugs that inhibit the senescence-associated secretory program (SASP)

LEVERAGING SENESCENCE THERAPEUTICALLY

Senescence Inducers

While many commonly used cancer therapies are known senescence inducers, it remains unclear why they induce senescence in some settings and not others. Genetic or other molecular biomarkers that predict the propensity of cancer cells to become senescent are needed. In addition, it is not yet clear what fraction of senescent cell induction is necessary to produce an effective response in human cancers, or whether there is a bystander effect through which senescent cells might impact nonsenescent cells in the tumor.

As mentioned previously, one major limitation of senescence-inducing conventional anticancer therapies is that they often trigger senescence in normal cells as well, leading to side effects. New therapeutics that specifically induce senescence in cancer cells, and particularly those that stimulate immune surveillance, are particularly desirable. Nevertheless, most assays to test or screen for cancer therapeutics use short-term proliferation and viability assays that do not assess senescence induction, which arises over time and requires high-content measurements beyond mere proliferation (Wang et al. 2022). Drugs that specifically target mutated proteins or pathways may achieve such effects, and indeed, oncogenic BRAF inhibitors can produce a prominent SASP response in *BRAF*-mutant melanoma (Grimm et al. 2018).

Efforts are underway to develop more effective screening approaches such as syngeneic senescence-proficient and -deficient screening models and fluorescent senescence reporters (Aarts et al. 2017, Tordella et al. 2016, Wang et al. 2017). Algorithms are being developed to facilitate the identification of senescent cells in high-content screening platforms (Gorgoulis et al. 2019). Early work indicates that such approaches are feasible (Kusumoto et al. 2021).

Owing to the dual effects of senescence on tissue biology, senescence inducers that provoke immune surveillance are highly preferable to those that do not. While immune and tumor cell coculture-based screening is laborious, benefits include assessment of the desired functional phenotype (i.e., immune-mediated tumor cell targeting) alongside the ability to identify SASP modulators. These screening methodologies will facilitate the development of precision senescence inducers, i.e., therapies that leverage the cancer cell genetic and epigenetic state to selectively induce senescence.

Senotherapies

As many of the detrimental effects of senescence are associated with the accumulation of senescent cells, there is significant interest in developing senotherapies, or drugs that target senescent cells. Senolytics and senomorphics are the two major classes of senotherapies: senolytics selectively kill senescent cells, whereas senomorphics inhibit the SASP. The potential utility of targeting senescent cells was first established in a proof-of-concept study by Baker et al. (2011), who demonstrated that lifelong senescent cell clearance can delay the onset of age-related pathologies. Furthermore, selective senescent cell clearance in older mice attenuates progression of already established age-related disorders including metabolic dysfunction (Baker et al. 2011, 2016; Xu et al. 2015; Zhu et al. 2015). Similar studies have subsequently shown that eliminating senescent cells from damaged tissues improves pathologies ranging from osteoarthritis to lung disease, atherosclerosis, and even metabolic disorders including diabetes and cachexia (von Kobbe 2019). Not surprisingly, these observations have stimulated great interest in developing senolytic therapies for the treatment of senescence-associated pathologies.

Senolytic CAR T cells: chimeric antigen receptor (CAR) T cells genetically engineered to target and kill senescent cells

While most efforts aim to alleviate pathologies associated with chronic tissue damage, there are emerging cancer indications as well. These include attempts to ameliorate the side effects of cancer therapy by eliminating senescent cells that accumulate following cancer therapy or to reduce the cancer-promoting effects of inflammatory environments (Prasanna et al. 2021). Indeed, senolytics can alleviate several short- and long-term effects of doxorubicin toxicity (e.g., bone marrow suppression, cardiac dysfunction, and decreased activity and strength) and radiation (e.g., lung fibrosis, ulcers, xerostomia, physical dysfunction, and frailty) in addition to cisplatin-induced peripheral neuropathy and bleomycin-induced pulmonary fibrosis (Wang et al. 2022).

Senolytics

Most senolytics currently in use are repurposed cancer drugs, including histone deacetylase (HDAC) inhibitors (panobinostat and valproic acid), tyrosine kinase inhibitors (dasatinib), PI3K/AKT/mTOR inhibitors (quercetin and fisetin), and BCL-X_L or BCL2 inhibitors (navitoclax and venetoclax) (Kirkland & Tchkonia 2020, Prasanna et al. 2021, Wang et al. 2022, Zhang et al. 2021). Unfortunately, for many of these agents, the precise mechanism leading to senolysis is not entirely clear. One notable exception is BCL2 family inhibitors, which exploit the higher dependency of some senescent cells on BCL-2 family proteins to maintain their survival (Yosef et al. 2016). Indeed, navitoclax (ABT-263), a dual BCL-X_L and BCL2 inhibitor, has shown promising senolytic activity in preclinical studies, although its clinical development has been hampered by dose-limiting thrombocytopenia (Chang et al. 2016, Kaefer et al. 2014, Mason et al. 2007). Beyond cancer drugs, two recent studies suggest that cardiac glycosides can be repurposed as senolytic agents (Guerrero et al. 2019, Triana-Martinez et al. 2019).

Efforts are also underway to improve the specificity of senolytics in targeting senescent cells. One example of this approach is DT22160, a proteolysis-targeting chimera (PROTAC) version of navitoclax that stimulates degradation of BCL-X_L via the VHL (Von Hippel–Lindau) E3 ligase that is not expressed in platelets, circumventing a key dose-limiting toxicity (He et al. 2020, Khan et al. 2019). Another targeting strategy takes advantage of high levels of β-galactosidase in senescent cells to activate galactose-conjugated navitoclax prodrugs, also reducing systemic toxicity (Galiana et al. 2020, González-Gualda et al. 2020). PROTAC BET inhibitors and additional galactose-conjugated prodrugs such as galactose-modified duocarmycin are currently under investigation (Guerrero et al. 2020, Wakita et al. 2020).

Senolytic approaches are also moving beyond small molecules. For example, CAR (chimeric antigen receptor) T cells targeting uPAR (urokinase-type plasminogen activator receptor), a cell surface protein that is broadly induced during senescence, can potently eliminate senescent cells from tissues (Amor et al. 2020). A senolytic vaccine targeting GPNMB (glycoprotein nonmetastatic melanoma protein B) was recently developed and appears to be effective in animal models (Suda et al. 2021).

Senomorphics

Established senomorphs include inhibitors of NF-κB, ATM, BET, STING, p38/MAPK, and mTOR (Sun et al. 2019). In some settings, senomorphic drugs may contribute to therapy resistance: BET and STING inhibitors also limit beneficial antitumor immune responses. In contrast, p38/MAPK inhibition and IL-8 blockade have been shown to potentiate antitumor immune responses (Dominguez et al. 2017, Dou et al. 2017, Pereira et al. 2019, Tasdemir et al. 2016). Just as the SASP can have paradoxical effects depending on the context, the same seemingly holds true for senomorphs, further underscoring the need for predictive biomarkers of senescence output and response.

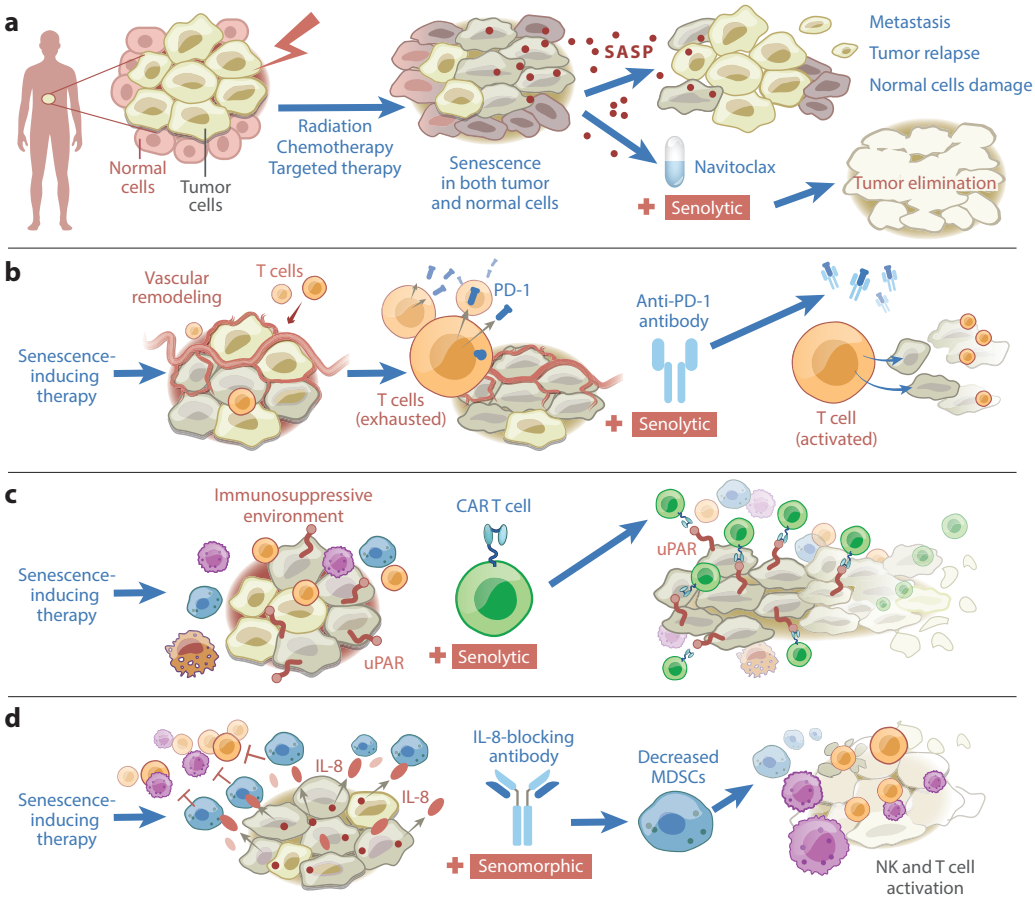

Figure 3

Leveraging senescence therapeutically. One-two punch therapy leverages the beneficial effects of senescence induction (i.e., the first punch) while eliminating liabilities associated with lingering senescent cells (i.e., the senotherapies as the second punch). Second-punch senotherapies can include senolytic small-molecule inhibitors, such as navitoclax (*a*); senolytic immune-modulatory agents, such as PD-1 blockade (*b*); so-called synthetic immune cell therapies, such as senolytic CAR T cells (*c*); and senomorphics such as IL-8-blocking antibodies (*d*). In addition to improving treatment response and decreasing metastases, senotherapies have the potential to reduce the deleterious effects of therapy-induced senescence on normal tissues. Abbreviations: CAR, chimeric antigen receptor; MDSCs, myeloid-derived suppressor cells; NK, natural killer; SASP, senescence-associated secretory phenotype; uPAR, urokinase-type plasminogen activator receptor.

One-Two Punch Therapy Combinations

One conceptually novel rationale for combination cancer therapy harnesses vulnerabilities produced by the senescent state to facilitate cancer cell elimination. This strategy, often referred to as the one-two punch, was delineated by René Bernards and involves combining a senescence-inducing agent with a senolytic agent to drive tumor regression (**Figure 3**) (Wang et al. 2022). In addition to increasing treatment efficacy, this approach may also reduce the deleterious effects of therapy-induced senescence on normal tissues. Moreover, because senescence induction takes time, administration of the senescence-inducing and senolytic agents may be temporally separable, reducing the potential for combined toxicities.

One-two punch therapy: the combination of senescence-inducing and senescence-eliminating therapies

Preclinical data suggest that such combination strategies can be effective. For example, the senolytic HDAC inhibitors panobinostat and valproic acid can synergize with chemotherapy to eliminate chemotherapy-resistant senescent tumor cells that accumulate during treatment, delaying relapse, reducing metastasis, and improving survival (Demaria et al. 2017, Di Micco et al. 2011, Samaraweera et al. 2017). Similarly, a senolytic strategy targeting the metabolic demands of chemotherapy-induced senescence promoted tumor regression and improved survival in the murine *Eμ-Myc* lymphoma model (Dorr et al. 2013). Navitoclax has shown promise in combination with many senescence-inducing chemotherapies (**Figure 3*a***) (Fleury et al. 2019, Saleh et al. 2020b, Wang et al. 2017). The senolytic mTOR inhibitors temsirolimus, AZD2014, and AZD8055 have activity when combined with docetaxel and XL413, a CDC7 inhibitor, in prostate and liver cancer, respectively (Fung et al. 2009, C. Wang et al. 2019). Senolytics such as navitoclax, venetoclax, and the cocktail dasatinib plus quercetin have also shown promise as radiation sensitizers and appear to suppress tumor invasiveness and metastasis (Fletcher-Sananikone et al. 2021, Nicolas et al. 2022, H. Wang et al. 2019). Nonetheless, because many of these agents were designed to target cancer cells through non-senescence-related mechanisms, it can be challenging to unravel whether the combinatorial effects are due to senolysis or some other anticancer activity.

While many of the one-two combination strategies under development use small molecules that exploit cell-intrinsic vulnerabilities associated with senescence, immune cells including NK cells and $CD8^+$ T cells also have the potential to naturally eliminate senescent cells. Moreover, certain senescence-inducing cytotoxic and targeted agents can drive tumor regression through immune-mediated senolysis. In these settings, senescence induction is an unappreciated form of immuno-oncology.

At least in some contexts, therapy-induced senescence can provoke immune responses against the tumor or create a more inflamed (hot) tumor environment. For example, in immunocompetent murine models of pancreas cancer, the synergistic activity of anti-PD-1 together with the senescence-inducing combination of CDK 4/6 and MEK inhibitors involves SASP-mediated remodeling of the tumor environment that enables a $CD8^+$ T cell response against senescent tumor cells. Interestingly, synergy between conventional therapies and immune checkpoint blockade has also been noted in various preclinical and clinical studies, which may also serendipitously reflect a one-two punch mechanism (**Figure 3*b***) (Jerby-Arnon et al. 2018, Ruscetti et al. 2020). Here, anti-PD-1 acts as a senolytic agent.

While senescent cells do not always trigger an immune surveillance response, so-called synthetic immune cells or immune-modulatory agents that potentiate immune cell targeting can enhance the activity of senescence-inducing agents. For example, a proof-of-concept study shows that senolytic CAR T cells synergize with MEK/CDK 4 inhibitor combinations in a lung cancer model (**Figure 3*c***) (Amor et al. 2020). Similarly, senomorphs such as BMS-986253, an IL-8-blocking antibody in clinical development, may be an effective second punch (**Figure 3*d***) (Bilusic et al. 2019). Other work has demonstrated the potential of antibody-drug conjugates targeting proteins upregulated during senescence as senolytic agents (Poblocka et al. 2021). Other potential immune-modulatory senolytics include CAR NK cells, bispecific T cell engagers, and other factors to awaken exhausted T cells or stimulate an NK cell response.

Together, the abovementioned preclinical studies provide a rationale for the clinical development of combination one-two punch therapies for cancer treatment. The recently held National Cancer Institute Workshop on Radiation, Senescence, and Cancer included extensive discussion of the clinical utility of one-two punch therapy, highlighting its potential to improve patient outcomes (Prasanna et al. 2021). Still, questions remain. Do combinatorial one-two punch therapies

show improved efficacy compared to individual agents? Does efficacy vary by context, and if so, why? Are combinatorial drug therapies toxic, and if so, can alterative treatment strategies be developed to minimize toxicity while maintaining efficacy? Research addressing these questions will be required to add senescence-modulating therapies to the arsenal of precision cancer therapeutics.

CLINICAL DEVELOPMENT OF SENOTHERAPIES

Given the powerful effects of senescence induction on antitumor response seen in preclinical studies, it is surprising that so little is known about the contribution of therapy-induced senescence to treatment outcomes in the clinic. As mentioned previously, radiation and a range of cytotoxic agents can induce senescence in tumor cell lines in vitro, and in clinical settings there are abundant data collected over decades on molecular or genetic factors that can influence treatment outcome. Still, there have been few if any systematic studies to examine whether the response of these therapies has anything to do with their prosenescence activity, in part because senescence markers in tumor cells are not well defined and on-treatment biopsies are often limiting. Nonetheless, therapy-induced senescence was identified in 40% of posttreatment surgical specimens in two independent studies in breast cancer patients treated with neoadjuvant cyclophosphamide-based chemotherapy regimens (Saleh et al. 2021, te Poele et al. 2002). Similarly, therapy-induced senescence was identified in lung cancer patients treated with neoadjuvant carboplatin/taxol, but not in treatment-naïve patients taken directly to surgery (Roberson et al. 2005).

A variety of targeted therapies can also induce senescence, although few were designed with this intention. These include cell cycle inhibitors, BCR-ABL, Aurora kinase, EGFR, BRAF, MEK, and even VEGF (Chibaya et al. 2022, Haferkamp et al. 2013, Lee et al. 2017, Saleh et al. 2020a). Some of these inhibitors are thought to induce senescence through DNA damage; for example, Aurora kinase inhibitors block chromosomal segregation in mitosis, leading to DNA damage and senescence (Chibaya et al. 2022). Others such as CDK 4/6 cell cycle inhibitors block G1/S phase transition by preventing CDK 4 and CDK 6 kinase–dependent pRb phosphorylation, sequestering E2F transcription factors and inducing G1 arrest and senescence (Chibaya et al. 2022). Despite many of these inhibitors being commonly used clinically, studies evaluating the contribution of senescence to their therapeutic efficacy are lacking.

There is significant interest in the clinical development of senotherapies, although most current efforts are focused on noncancer indications (Dolgin 2020). The senolytic combination of dasatinib and quercetin appears safe and reduces senescent cell burden in humans (Hickson et al. 2019, Justice et al. 2019). Fisetin and dasatinib are being studied in age-associated pathologies such as chronic kidney disease, skeletal health, and Alzheimer's and other neurological disorders (Lee et al. 2017, Prasanna et al. 2021). As preclinical studies indicate that senotherapies may also ameliorate side effects of nonspecific senescence inducers, clinical trials in this area are expected. St. Jude Children's Research Hospital is leading the SEN-SURVIVORS trial evaluating fisetin alone and dasatinib with quercetin to reduce senescence and improve frailty in adult survivors of childhood cancer (**http://clinicaltrials.gov** identifier NCT04733534).

Senolytic development has not been completely smooth sailing: For example, UBX0101, a p53/MDM2 interaction inhibitor, was recently abandoned after a placebo-controlled randomized phase II trial reported lack of efficacy in patients with painful osteoarthritis (NCT04129944). Given the importance of p53 in promoting senescence in many contexts, it remains to be determined whether the effects were a failure of the drug or the concept. Suggesting the latter, a recent phase I trial evaluating a BCL-X_L-targeting senolytic UBX1325 showed improved visual acuity in the majority of patients with advanced diabetic macular edema or wet age-related macular degeneration (NCT04537884) (Bhisitkul et al. 2022).

Few trials of senolytics in cancer have been initiated. Navitoclax and temsirolimus are being evaluated in combination with the senescence inducer rituximab in hematological malignancies (Dabritz et al. 2016, Wang et al. 2022). Navitoclax is also being evaluated in combination with various chemotherapy agents, including etoposide, irinotecan, cisplatin, gemcitabine, paclitaxel, and docetaxel in various solid tumor malignancies (Wang et al. 2022). The safety and tolerability of DT2216 is being evaluated in a phase I trial for patients with relapsed or refractory solid tumors (NCT04886622). While this trial does not incorporate senescence-inducing therapy, trials of such combinatorial strategies will likely be initiated following the establishment of DT2216's safety.

Despite the paucity of rationally designed studies, a range of clinical trials are testing the concept by combining known senescence inducers with senolytic agents, particularly immunotherapies. Multiple trials have improved clinical outcomes with the addition of immune checkpoint blockade to chemotherapy or radiation therapy. In patients with metastatic non-small-cell lung cancer, the addition of anti-PD-1 therapy to pemetrexed-platinum chemotherapy significantly improved progression-free survival (PFS) and overall survival (OS) (Gadgeel et al. 2020). In melanoma, improved PFS was reported with the addition of an anti-PD-L1 agent to combined BRAF and MEK inhibition (Gutzmer et al. 2020). The KEYNOTE-001 trial demonstrated improved PFS and OS with PD-1 blockade in patients previously treated with radiation as compared to radiation-naïve patients (Shaverdian et al. 2017). Not all trials have supported the efficacy of this approach; trials in head and neck cancer (JAVELIN) and cervical cancer (CALLA) have found no improvement in PFS when adding PD-1 blockade to concurrent chemoradiation (Kemp 2022, Lee et al. 2021).

Recent mouse studies suggest that the sequencing of radiation and PD-1 blockade is important, finding improved outcomes when PD-1 blockade is administered after radiation (Wei et al. 2021). In addition, PD-(L)1-blocking antibodies are being evaluated in multiple ongoing trials in combination with senescence-inducing therapies such as CDK 4/6 inhibitors in breast cancer (Wang et al. 2022). Still, since most studies are not actively examining senescence induction and elimination of senescent cells in patients, interpretation of their results is difficult.

CHALLENGES AND NEEDS

While there is much excitement surrounding the potential of exploiting senescence biology for cancer therapy, the development of rational senescence-modulating strategies has been hampered by our incomplete understanding of senescence mechanisms and lack of precise biomarkers that predict response. Indeed, while much is known about senescence mechanisms in normal cells, the impact of cancer-associated mutations on the ability of various senescence inducers to induce specific senescent states in cancer cells remains poorly understood. Emerging evidence suggests that senescent states can be heterogeneous, potentially involving a range of arrest mechanisms, epigenetic programs, and SASP profiles that may influence strategies to induce or eliminate senescent cells. Understanding the mechanisms by which senescent cells become visible to the immune system will be critical to the development of therapeutic strategies to promote antitumor immunity and avoid the protumor effects of senescence.

While senescence-inducing therapies and one-two punch combinations with senolytics hold promise, it remains to be determined what fraction of cells within a tumor undergo senescence in response to various therapeutics and whether senescence induction in a subset of tumor cells triggers a bystander effect. Such information is important because failure to induce senescence in all tumor cells might lead to tumor progression or blunt the ability of a senolytic to drive tumor regression. Still, if senescent cells trigger a bystander effect that alters nonsenescent cells or creates an immunologically hot tumor microenvironment, it may not be necessary to drive all tumor

cells into senescence to achieve substantial therapeutic benefit. Answering these questions will not be easy and requires matched pre-, on-, and posttreatment biopsies. Further complicating the analysis, accurate quantification of senescent cells in tissues can be confounded by their immune-mediated clearance.

There remain few systematic approaches to identify and characterize senescence induction and senescent cell clearance in vivo (Gorgoulis et al. 2019). Moreover, challenges in obtaining relevant on-treatment biopsies make it difficult to measure the accumulation of senescent cells or their elimination posttreatment. As such, it will be essential to develop noninvasive senescence biomarkers via analysis of blood or radiologic imaging (Iske et al. 2020, Lozano-Torres et al. 2017).

PERSPECTIVE

Further insights into senescence mechanisms, the signals that trigger its induction, and the evolution of tumor cells that have bypassed senescence will teach us much about the forces at play during early tumorigenesis. Additionally, further insights into the physiological roles and regulation of senescence and how they are co-opted for tumor suppression, or derailed to trigger tissue decline, will have a profound impact on our understanding of human disease. The ability of senescent cells to influence tissue biology connects a broad range of pathologies that are often distinct, and as such, a better understanding of how senescence operates in normal tissues provides promise for therapeutic approaches that target multiple morbidities.

While developing tumor cells find strategies to avoid senescence, therapeutic induction of senescence in tumor cells can produce marked changes to tumor cells and their environment. While this program is initially cytostatic, it can coordinate epithelial and stromal responses that, in some settings, recapitulate aspects of physiological wound healing and lead to tumor involution. In such settings, senescence induction also represents a novel strategy in immune oncology whose further understanding holds great therapeutic potential. Still, our knowledge of the heterogeneity of senescent states is underdeveloped, and we are not yet able to predict the output of a senescence trigger in different cell and tissue contexts. Systematic studies of senescent states will yield an understanding of the cellular, tissue, and systemic factors that determine the effects of senescence and will allow senescence biology to be harnessed to improve patient outcomes.

SUMMARY POINTS

1. Cellular senescence is a potent tumor-suppressive mechanism that prevents tumor development and can contribute to the anticancer activity of some cancer treatments.
2. The senescence program is a two-component process that couples stable proliferative arrest to a secretory program that influences the tissue environment.
3. Excess senescent cells accumulate in aged and damaged tissues and following treatment with common cancer therapies.
4. In some contexts, senescent cells are removed by the immune system, promoting tissue repair and regeneration, whereas in others they persist and promote tissue decline.
5. Senescent states are likely heterogeneous, leading to different effects on tissue biology.
6. Senescence-inducing agents can stimulate an immune response against the tumor, leading to outright tumor rejection or increased sensitization to immune checkpoint blockade.

7. Senolytic therapies stimulate removal of senescent cells when the immune system fails to do so and are in development for a range of human pathologies, including cancer.
8. Increasing the cancer cell selectivity of senescence-inducing therapies may improve their therapeutic index or increase their synergy with senolytic agents.

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