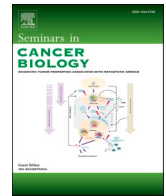




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Biological functions of therapy-induced senescence in cancer

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ABSTRACT

Therapy-induced cellular senescence is a state of stable growth arrest induced by common cancer treatments such as chemotherapy and radiation. In an oncogenic context, therapy-induced senescence can have different consequences. By blocking cellular proliferation and by facilitating immune cell infiltration, it functions as tumor suppressive mechanism. By fueling the proliferation of bystander cells and facilitating metastasis, it acts as a tumor promoting factor. This dual role is mainly attributed to the differential expression and secretion of a set of pro-inflammatory cytokines and tissue remodeling factors, collectively known as the Senescence-Associated Secretory Phenotype (SASP). Here, we describe cell-autonomous and non-cell-autonomous mechanisms that senescent cells activate in response to chemotherapy and radiation leading to tumor suppression and tumor promotion. We present the current state of knowledge on the stimuli that affect the activation of these opposing mechanisms and the effect of senescent cells on their micro-environment eg. by regulating the functions of immune cells in tumor clearance as well as strategies to eliminate senescent tumor cells before exerting their deleterious side-effects.

1. Introduction

Cellular senescence is a state of stable cell cycle growth arrest where cells remain metabolically active and do not respond to extracellular growth signals. Senescent cells often present an enlarged and flattened morphology, an altered metabolism, and dysfunctional mitochondria [1]. They stain positive for the lysosomal enzyme senescence-associated β galactosidase (SA- β -gal) at pH 6, which was the first marker utilized for their identification [2]. On a molecular level, upregulation of the tumor suppressor p16^{INK4a} is one of the most common hallmarks of senescent cells and frequently used biomarkers used *in vitro* and *in vivo*, reviewed by [3]. In addition, activation of the p53/p21^{WAF1/Cip1} pathway and downregulation of the nuclear lamina protein lamin B1 are common features of the senescent phenotype [4,5]. Furthermore, senescence inducers that cause DNA damage lead to the formation of DNA damage foci known as DNA-SCARS (DNA segments with chromatin alterations reinforcing senescence), while some cells form Senescence-Associated Heterochromatin Foci (SAHF), all of which detectable using

immunostaining techniques [6]. Senescent cells are also characterized by their ability to secrete a plethora of cytokines, growth factors and proteases that can affect neighboring cells, known as the Senescence-Associated Secretory Phenotype (SASP) [7]. Currently, none of these markers is considered to be universal, and senescence identification needs to be achieved via the combination of different measurements.

Transient accumulation of senescent cells has been shown to be important for tissue remodeling and repair processes during embryogenesis and adulthood [8,9]. However, senescent cells accumulate and persist during organismal aging across different species [10–13], where they play a role in the development of various age-related pathologies. In agreement with this notion, their elimination reverses many pathological conditions and improves the health- and lifespan [14–22]. Their accumulation can result from intrinsic factors, such as telomere shortening (also known as replicative senescence) or oncogenic mutation (oncogene-induced senescence, OIS) [23], or from extrinsic sources, including ionizing and non-ionizing radiation or chemotherapeutic

Abbreviations: CDK, cyclin-dependent kinase; EFN, ephrin; IFN- γ , interferon γ ; IGF, insulin growth factor; IL, interleukin; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; NK cells, natural killer cells; NSCLC, non-small cell lung cancer; OIS, oncogene-induced senescence; ROS, reactive oxygen species; SA- β -gal, senescence-associated beta galactosidase; SASP, senescence-associated secretory phenotype; TIS, therapy-induced senescence; TNF- α , tumor necrosis factors α .

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drugs. In an oncologic context, cellular senescence induced by exposure to chemotherapeutic drugs or irradiation is referred to as therapy-induced senescence (TIS) and displays both anti- and pro-tumorigenic properties [24]. Although the aim of these therapies is to induce cell death and senescence in the cancer cells being treated, dividing stromal cells are also affected, resulting in TIS stromal cells that are capable of influencing their microenvironment via the SASP.

The SASP exerts complex effects via the secretion of proteins that may signal back to receptors on their own cell surface (cell autonomous) or on the surface of other cells (non-cell autonomous). This complexity is further increased by the differential effects a single protein may exert in a cell-autonomous compared to a non-cell autonomous manner. The aim of this review is to describe beneficial and detrimental effects of TIS in cancer and the specific roles of canonical TIS-SASP factors.

2. Cell autonomous roles

Senescence has been long considered a tumor-suppressing mechanism activated upon stress that prevents transformation of pre-malignant lesions or uncontrolled proliferation of fully transformed cells [25,26]. For this reason, studies have repetitively shown that induction of senescence is a desirable outcome of cancer therapy and a predictor of treatment efficacy. Using an *in vivo* model of B cell lymphoma, Schmitt et al., showed that cyclophosphamide-induced senescence in cancer cells requires active p16 and p53 pathways and improves prognosis and survival in mice [27]. te Poele et al., were the first to detect senescent cells after chemotherapy treatment in human breast cancer samples, but not in normal surrounding tissue, and to show that treatment of cancer cells with the topoisomerase inhibitors SN-38 and etoposide induces senescence that needs p53 activation for its establishment and p16 for maintenance [28]. *In vitro* studies of different human cancer cell lines, including breast, colon and prostate, showed that treatment with doxorubicin or γ -irradiation induced senescence with increased SA- β -gal activity and was considered a favorable treatment outcome, given the fact that this stable growth arrest can be achieved with low drug doses that do not cause toxicity and side-effects [29]. TIS promoted by low doses of doxorubicin is associated with increased Reactive Oxygen Species (ROS) due to activation of the Ataxia-Telangiectasia-Mutated (ATM) and Ataxia Telangiectasia and Rad3-related (ATR) pathway and p53 signaling [30]. Epigenetic mechanisms may also play a role in the decision between senescence and apoptosis. Overexpression of the DNA methyltransferase DNMT3a can lead to cancer cells death in otherwise senescence-inducing doxorubicin doses via inhibition of p21 expression [31]. In colon carcinoma and fibrosarcoma lacking p16, the depletion of p21 and/or p53 did not completely abolish a senescent phenotype, indicating implication of additional factors [32,33]. Induction of senescence upon methotrexate treatment in breast cancer cells requires p53 activity, but the growth arrest was shown to be p53-independent [34]. Similarly, cisplatin-induced senescence can be induced in a p53-independent manner [35,36]. However, in non-small cell lung cancer (NSCLC), the co-treatment of cisplatin and dexamethasone (a common intervention to reduce chemotherapy side effects) abrogates the senescent phenotype in a p53- and NF- κ B-dependent manner, leading to reduced sensitivity to cisplatin and to increased tumor growth [35]. Although senescent cells are generally considered resistant to apoptosis, some TIS cancer cells can be more susceptible to apoptosis. Doxorubicin-induced senescent breast and lung cancer cells upregulate the expression of Fas via a NF- κ B-mediated upregulation of Tumor Necrosis Factor α (TNF- α) and Interferon γ (IFN- γ) [37].

Cyclin-Dependent Kinases 4/6 (CDK4/6) inhibitors are a new generation of chemotherapeutic drugs, mainly used for the treatment of breast cancer [38–40]. Prolonged treatment of melanoma cells with the CDK4/6 inhibitor palbociclib causes senescence induction and reduced sensitivity to vemurafenib, a drug used for tumors carrying the BrafV600E mutation, via mammalian target of rapamycin (mTOR)

inhibition. Senescence induction upon palbociclib treatment was also observed in vemurafenib-resistant melanoma in culture and *in vivo* and suggested to be a more potent and less toxic therapeutic solution compared to standard chemotherapy [41]. Both palbociclib and abemaciclib, another CDK4/6 inhibitor, induce senescence in preclinical models of breast cancer and can reduce tumor volume via activation of interferon-mediated immunosurveillance [42].

Aurora kinases are overexpressed in cancer and associated with poor survival rates, thus serving as potential therapeutic targets [43–45]. Treatment of colon cancer cells with the Aurora A kinase inhibitor MLN8054 promotes a stable growth arrest and senescent-like phenotype which includes enhanced SA- β -gal positivity and activation of the p53/p21 pathway [46]. Another Aurora A kinase inhibitor (AKI603) was shown to induce senescence in imatinib-resistant chronic myeloid leukemia cells through a p21-dependent pathway and upregulation of ROS, and synergize with BCR-ABL. However, induction of senescence during the combination treatment was not evaluated, despite a clear effect on reducing tumor growth *in vivo* [47]. Furthermore, the inhibitor MLN8237 induced senescence in a model of metastatic melanoma via p53-independent but ATM/Chk2-dependent mechanisms [48], and sensitized melanoma cell to TNF-related apoptosis-inducing ligand (TRAIL)-induced cytotoxicity via upregulation of Death Receptor 5 (DR5) and downregulation of decoy receptors [49]. Similar results were obtained in a model of lung cancer, where MLN8237 induced a p53-dependent senescence state and sensitized tumor cells to radiation. However, senescence induction was evaluated only by using morphological features, and a more comprehensive biochemical and/or molecular characterization is missing [50]. To conclude, standard chemotherapeutic drugs, but also new generation drugs can induce senescence in different cancer models and limit tumor growth, but the mechanisms involved are diverse. Main senescence pathways like p53/p21 are not always involved, while the mechanisms governing tumor reduction can also be different including apoptosis or immune-mediated killing.

In colon adenomas and carcinomas, spontaneous senescence induction resulted in longer progression-free survival period after treatment with 5-fluorouracil/leucovorin in comparison to non-senescent tumors [51]. Another finding of this study was that adenomas had higher senescence levels compared to more aggressive carcinomas, a phenomenon also observed in rat mammary tumor samples after treatment with tamoxifen [52]. This is reminiscent of OIS, where senescent cells are visible in pre-neoplastic lesions but not in invasive specimens, supporting the essential role of senescence as a barrier to tumor progression [53–58]. These studies also highlight the importance of p53 for senescence induction, as its inhibition leads to tumor formation while its restoration induces senescence [54,55,58,59].

On the other hand, TIS can promote tumor progression through apoptosis resistance, dormancy, and relapse. Several studies have shown that prolonged culture of TIS cells causes increased expression of stemness markers and escape from cell cycle arrest of some pseudosenescent cells reviewed in [60–62]. Reversibility of senescence was observed in human fibroblasts treated with etoposide and camptothecin, although cells grew more slowly after reversal [63]. In p53 and p16-null NSCLC cells, treatment with different chemotherapeutic drugs leads to G2/M growth arrest, activation of the ATM pathway and a senescence phenotype which soon after treatment was reversed due to phosphorylation and activation of the ATM target cdk1 (known also as cdc2) [64]. Survivin, a cdc2/cdk1 target, appears to be an important mediator of this phenomenon, as its expression was shown to be necessary for senescence induction and for subsequent cell cycle re-entry [65]. Increased levels of cdc2 were also detected in a breast cancer model after treatment with doxorubicin in clones that were resistant to doxorubicin- and γ -irradiation-induced senescence, indicating that this protein may play a role in the evasion and escape from senescence [66]. Another important mechanism underlying cell cycle re-entry is polyploidy and aneuploidy. After doxorubicin treatment, senescence escape was

observed in senescent colon cancer cells that develop aneuploidy, but not in breast cancer cells without aneuploidy. Aneuploidy was accompanied by increased ROS levels and use of antioxidants reduced the number of escaper cells [67]. The phenotypic association of aneuploidy and senescence escape has been recently described elsewhere [68,69]. Senescent colon cancer HCT116 cells were also found to express the stem cell marker NANOG and re-enter proliferation [70]. Similar observations were made in lymphoma models treated with doxorubicin, where senescence was induced but cells resumed proliferation and expressed stem cell markers (eg. β -catenin) and induced lymphomas more aggressively in mice compared to cells that were never senescent. Interestingly, it was also shown that senescent cells can be reprogrammed to express stem cell markers [71]. Etoposide treatment can also induce reversible senescence in lung and colon cancer cells. Etoposide or doxorubicin-treated lung and breast cancer cells are able to form tumors *in vivo*, but their growth rate was slower in immunocompetent mice, highlighting the importance of immunosurveillance mechanisms potentially activated by senescence-associated phenotypes and the SASP [72].

Although wild-type p53 is considered a positive indicator of treatment outcome, there are cases where an opposite effect is observed. In human breast tumors that were transplanted in mice and treated with a combination of epirubicin and cyclophosphamide, tumors carrying

wild-type p53 entered senescence, while tumors with mutated p53 went into mitotic catastrophe and presented higher overall pathological response. Senescence induction was associated with resistance to therapy and possible cell cycle re-entry upon completion of therapy [73]. These data may explain why breast cancer patients with mutated p53 had better responses and favorable outcomes after treatment [73–75]. Similar results were obtained in a mammary breast cancer model, where p53-mutated tumors maintained proliferation and eventually died after doxorubicin treatment causing delayed apoptosis [76,77]. Conversely, the presence of wild-type p53 induced senescence and produced cytokines including Eotaxin and Chemokine (C-C motif) ligand 5 (CCL5), that acted in an autocrine and paracrine manner leading to proliferation of neighboring cells and tumor relapse [77]. p21 prolonged expression after senescence induction can also cause senescence escape of cancerous and pre-cancerous cells. Its p53-independent accumulation causes cells to re-enter replication and become more aggressive, highlighting the importance of monitoring chemotherapeutic drugs that induce senescence and p21 upregulation [78]. In summary, TIS in an oncogenic context is highly complex. Although it can limit tumor growth, it can also be tumor promoting. Data suggest that, on the one hand, senescence limits tumor growth by arresting cancer cell growth. On the other hand, it can protect non-dividing cancer cells by limiting the effect of chemotherapeutic drugs that act during replication or may

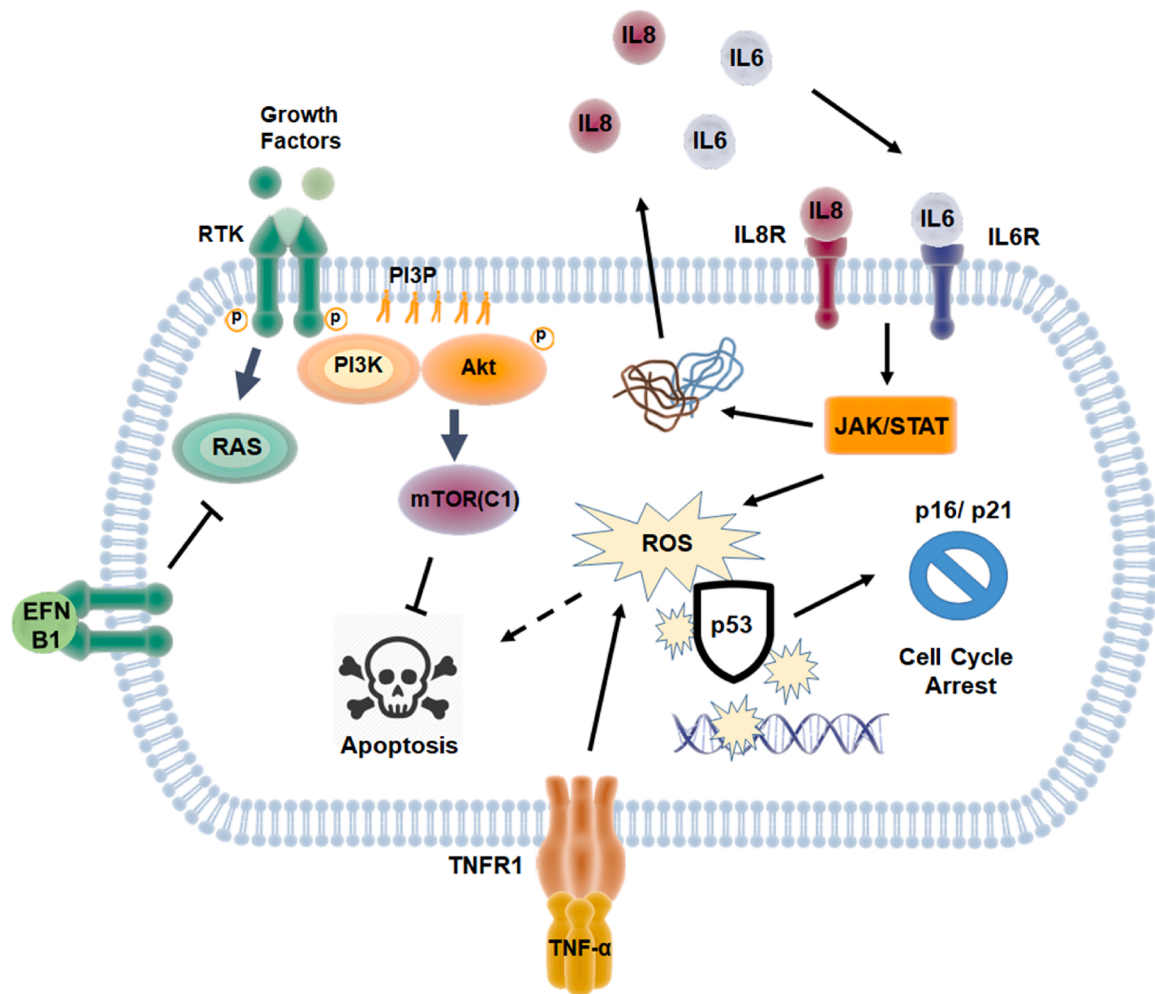


Fig. 1. Cell autonomous signaling of the SASP in therapy-induced senescent cells. Components of the SASP may exert autocrine effects by binding to the receptor of the secreting cell. For instance, secreted growth factors that fuel the proliferation of bystander cells, may also promote cell survival by inhibiting apoptosis (RTK/PI3K/Akt). Pro-inflammatory SASP factors can also act on an autocrine loop to help reinforce growth arrest (e.g. IL-6, IL-8, TNF- α), by increasing ROS production, activating the DNA Damage Response, and upregulating cyclin dependent kinase inhibitors (p16, p21). EFN, Ephrin; JAK/STAT, Janus kinase/signal transducer and activator of transcription protein; IL, Interleukin; mTOR(C1), mammalian target of rapamycin (complex 1); PI3K, Phosphoinositide 3-kinase; PI3P, Phosphatidylinositol 3-phosphate; ROS, Reactive Oxygen Species; RTK, Receptor tyrosine kinase; TNF- α , Tumor Necrosis Factor α .

render them resistant to apoptosis. These surviving cells could then re-enter the cell cycle and lead to tumor relapse. Since senescence is defined as a stable growth arrest, it is not clear whether these TIS cancer cells are actually senescent and develop mechanisms to bypass it [61,62] or pseudo-senescent, acquiring only an intermediate senescence-reversible state [79].

3. Non-cell autonomous roles

As described in the previous section, TIS often leads to tumor regression reviewed by [24]. However, TIS cells can persist after treatment and contribute to the adverse effects of chemotherapy and to cancer relapse via the SASP [80–84].

The non-cell autonomous function of senescent cells in a tumor setting remain highly complex, as the action of secreted factors depends on the target cell and the tissue microenvironment. Accumulation of certain SASP factors (e.g. IL-6, IL-8, TNF- α) autocrinally reinforces and paracrinally propagates the senescence-associated cell cycle arrest, thus limiting key steps for tumorigenesis such as tumor growth and angiogenesis (Fig. 1). Nevertheless, the same components may favor tumor progression by misbalancing inflammatory responses. Moreover, other SASP factors (e.g. VEGF, EGF, FGF) might paradoxically promote proliferation and angiogenesis in the surrounding tissue (Fig. 2). Thus, the actual outcome of generating TIS may be determined by multiple factors, such as the amount of the secreted components and their downstream sensitivity, as well as time-dependent differences in SASP components which may exacerbate in case of failure of the immune system to remove accumulating senescent cells.

In order to better understand these complex effects, below we describe non-cell autonomous roles of selected SASP factors and how

these may compare with their cell autonomous roles.

3.1. Chemokines and cytokines

3.1.1. IL-6 / IL-8

In a cell autonomous manner, Interleukin 6 (IL-6) is thought to reinforce cell cycle arrest of non-transformed cells by binding to IL-6R/CD126 in human fibroblasts [85]. The binding of the cytokine to its receptor and the adaptor protein GP130 results in Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling and increased protein translation of numerous proinflammatory factors, including IL-6 and IL-8, thereby resulting in a positive-feedback loop [86,87]. The expression of the IL-6 receptor is thought to be crucial in mediating the cell-autonomous vs non-cell autonomous effects of this cytokine, as the expression of the IL-6R is mostly limited to immune cell subsets (monocytes, megakaryocytes, leukocytes, and certain T-cell subpopulations), while endothelial cells and fibroblasts do not express the IL-6R [88]. However, the IL-6R is also upregulated in the senescent response, at least in oncogene activation, stress-induced, and cytokine-induced premature senescence [86,89,90]. In contrast, Glycoprotein 130 (GP130), the adaptor protein of IL6-R is widely expressed across cell types. Therefore, in a cell autonomous manner IL-6 may reinforce paracrine senescence. However, because the IL-6R is present in a soluble form in various inflammatory conditions, IL-6-STAT3 signaling may also help propagate the senescent phenotype, resulting in premature senescence of stromal cells [91]. In oncogenic contexts, IL-6 may therefore have a positive effect by stopping the proliferation of bystander cancer cells.

Similar to IL-6, IL-8 (also known as CXCL8) is similarly thought to reinforce cell cycle arrest of non-transformed cells in a cell autonomous

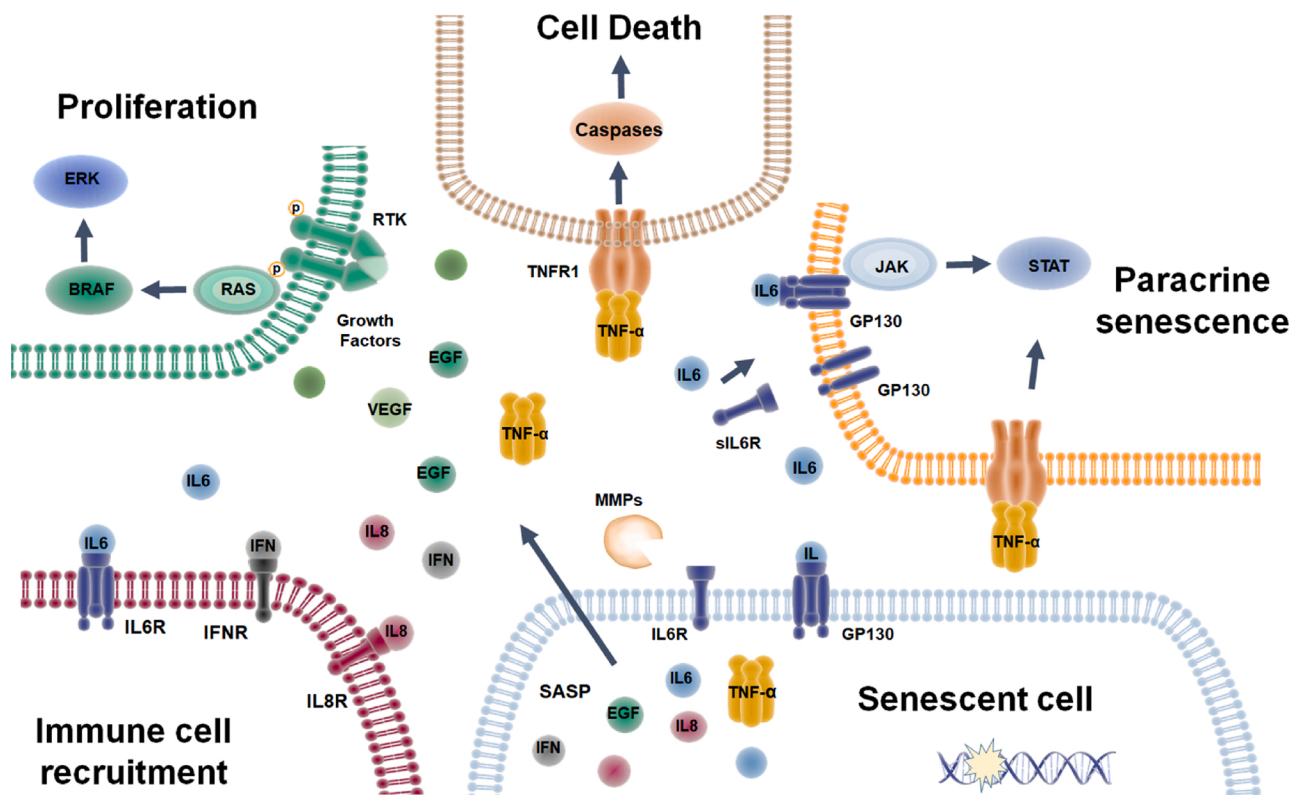


Fig. 2. Non-cell autonomous signaling of the SASP in therapy-induced senescent cells. Components of the SASP may exert paracrine effects by binding to the receptor of bystander cells. The effect of each factor will also depend on the target cell. In this way, secreted growth factors can fuel the proliferation of neighboring cells. Senescent cells factors can also promote immune cell recruitment through the release of cytokines and chemokines (IL-6, IL-8, IFN- γ), paracrine senescence (IL-6, TNF- α) or cell death (TNF- α). EFN, Ephrin; JAK/STAT, Janus kinase/signal transducer and activator of transcription protein; IL, Interleukin; mTOR(C1), mammalian target of rapamycin (complex 1); PI3K, Phosphoinositide 3-kinase; PI3P, Phosphatidylinositol 3-phosphate; ROS, Reactive Oxygen Species; RTK, Receptor tyrosine kinase; TNF- α , Tumor Necrosis Factor α .

manner, by binding to IL-8R/CXCR2/CD181 [85]. However, both IL-6, and more prominently IL-8, also plays a role as chemokine, in a non-cell autonomous manner, thus facilitating immune cell infiltration, and promoting an inflammatory response. This outcome may be beneficial in preneoplastic lesions, by facilitating immune cell-mediated tumor clearance, but may have negative consequences if sustained inflammation is unresolved. Supporting evidence includes senescent stromal cell-derived IL-6, shown to establish an immunosuppressive microenvironment driving tumor progression in an aged-skin model [92]. In addition, p38/MAPK-driven IL-6 and IL-8 release from senescent stromal cells can induce upregulation of the Natural Killer (NK) cell inhibitory ligand human leukocyte antigen E (HLA-E) in neighboring cells, resulting in immune evasion, a phenomenon also observed in aged human skin tissue [93].

3.1.2. *TNF- α / IFN- γ*

TNF- α is a potent pro-inflammatory cytokine with context dependent effects. As its name would suggest, it was initially identified due to its potent anti-cancer effects observed in a variety of tumoral tissues [94]. Later, studies have shown TNF- α to be involved in acute inflammatory responses and released in large amounts in response to IL-1 α , lipopolysaccharides and other bacterial products. In a cell-autonomous manner, TNF- α signaling initiates a STAT-dependent positive feedback loop, leading to a sustained interferon signaling, DNA damage, and cytokine secretion [95]. Therefore, TNF- α could be an early component of the SASP, similar to IL-1 α , and preceding other cytokines such as IL-6, IL-8, and IFN- γ .

In a non-cell autonomous manner, TNF- α may also be considered an inducer of paracrine senescence, at least in human endothelial cells in a ROS-dependent manner [95–97], as the use of ROS scavengers effectively inhibited senescence induction. Therefore, in addition to its tumoricidal activity, TNF- α may also prevent angiogenesis by stopping the proliferation of endothelial cells in tumor contexts. Similarly, IFN- γ has also been shown to induce cellular senescence through p53-dependent DNA damage signaling in human endothelial cells [98], while other type I interferons such as IFN- β are released in response to DNA-damage, promoting senescence and inhibiting hematopoietic stem cell function [99].

Moreover, non-cell autonomous roles for TNF- α and IFN- γ via interaction with immune cell subsets are widely described. Recently, the role of TNF- α -induced senescence and IFN- γ were shown to be essential for the immune clearance of pancreatic and B lymphoma cancer cells that survived an Immune Checkpoint Blockade [100]. However, despite the tentative use of TNF- α as an anti-cancer molecule, its use in the clinic has so far been hampered by its strong hepatotoxicity [101], while IFN- γ has been approved for the treatment of adult T cell leukemia in some countries [102], and continues to be studied as an adjuvant in vaccines and cancer immuno-therapies.

3.2. *Growth factors*

The expression of growth factors of various families such as the epidermal growth factor receptor family (EGF, TGF- α , amphiregulin), fibroblast growth factor family (FGF) or vascular endothelial growth factor family (VEGF) is widely documented in the secretory phenotype of TIS cells [7]. In a cell-autonomous manner, these growth factors may signal back to TIS cells through the PI3K/Akt/mTOR pathway [103, 104], thereby enhancing their survival. Furthermore, in a non-cell autonomous manner, they may exert proliferative effects via RAS/BRAF/ERK signaling, fueling the proliferation of bystander cells expressing the corresponding receptors. Both of these effects are considered deleterious in oncogenic contexts, and are therefore the target of a plethora of targeted anti-cancer drugs, often used in combination with chemotherapy or irradiation (e.g. EGFR inhibitors: erlotinib, gefitinib, lapatinib, and VEGF inhibitors: sorafenib, sunitinib, bevacizumab).

A recent study has identified the upregulation of ephrin (EFN)-dependent signaling in senescent stromal cells via the ephrin ligands EFN1 and EFN3 [104]. EFN signaling prevents cellular apoptosis in a cell-specific manner during embryonic development and tissue turnover [105]. In cancer cells, such as NSCLC, disrupting EFN3 signaling induces apoptosis and interferes with pro-survival networks [106]. Therefore, in a cell autonomous manner, ephrin signaling may prevent apoptosis and activate senescent cell pro-survival networks [107]. Conversely, in a non-cell autonomous manner, it may prevent apoptosis of neighboring cancer cells that have sustained DNA damage due to chemotherapy or radiation. Interestingly, EFN signaling may be disrupted by the promiscuous antioxidant quercetin, reported widely in the literature as a senolytic in combination with the PI3K tyrosine kinase and serpine inhibitor dasatinib [104]. In oncogenic settings, EFN receptor signaling may also block the RAS/BRAF/ERK pathway in a negative feedback loop [108].

3.3. *Matrix metalloproteinases*

Matrix metalloproteinases (MMPs) are a family of zinc-dependent proteases whose enzymatic activity is directed against components of the extracellular matrix (ECM), such as collagens, laminins, and proteoglycans. In normal contexts, MMPs help remodel the microenvironment via the degradation of the ECM, facilitating tissue remodeling and wound healing events. However, in oncogenic contexts, MMPs may facilitate metastasis by removing physical barriers to cell invasion and reducing cell-cell adhesion [109]. Upon exposure to the DNA-damaging agent bleomycin, senescent stromal fibroblasts increased the permeability of adjacent capillaries, thereby exposing nascent cancer cells to increased levels of mitogens, cytokines, and other plasma products, in an MMP-dependent manner [110].

Furthermore, MMPs can activate proteins released as inactive precursors. In oral cancers, the release of MMP-2 from senescent fibroblasts mediates pro-invasive functions via cleavage and activation of Transforming growth factor beta (TGF- β), a cytokine that promotes tissue repair and fibrosis via the upregulation of MMPs, including MMP-2, thereby resulting in a positive feedback loop [109].

In addition, MMPs may also cleave membrane receptors, and lead to release of soluble receptors such as IL-6R, thereby promoting paracrine senescence of stromal cells [91].

Lastly, they may also have deleterious effects in mounting immune responses via the cleavage of immuno-regulatory ligands present on the surface of damaged cells. In addition to avoiding immune cell recognition in a cell autonomous manner, the solubilized ligands may occupy and outcompete receptors in relevant immune cell types. Indeed, recently, the cell culture media of senescent fibroblasts and epithelial cells was shown to contain higher levels of soluble NKG2D ligands, accompanied by an upregulation of MMP-3. In agreement with these findings, the use of the broad-spectrum MMP inhibitor GM6001 effectively blocked ligand shedding and facilitated the elimination of persistent senescent cells by activated leukocytes [111]. Due to the proven roles of MMPs in early tumor progression, facilitating immune evasion and metastasis, several synthetic inhibitors have been developed over the last decades but failed in clinical trials, presumably due to their testing in advanced cancers, and due to a lack of specificity resulting in severe side effects (reviewed [112]). Nevertheless, the advent of specific inhibitors may raise new hopes in the treatment of early-stage tumors, in part through the removal of persistent senescent cells following adjuvant chemotherapy.

4. *Immuno-regulatory ligands*

As senescent cells elimination proceeds mainly via immune-mediated clearance, conditions of impaired immunosurveillance are associated to chronic senescence [113–115]. Senescent human fibroblasts and hepatic stellate cells (including etoposide-treated cells)

upregulate the NK ligands ULBP2 and MICA through extracellular signal-regulated kinase (ERK) activity and activate immune clearance [116]. In an oncogenic context, conditional p53 activation in liver carcinoma led to senescence induction and tumor regression through infiltration of NK cells, macrophages and neutrophils caused by the secretion of cytokines and adhesion molecules (Csf1, Mcl1, IL-15, and CXCL1, which shares a receptor with IL-8) [59]. Elimination of cancer cells seems to be mediated first by NK cells, since their blocking transiently interferes with tumor growth [117]. Activation of p53 has also been shown to increase expression of the NK ligand ULBP2 in human colon and breast cancer cells, where p53 mediates transcriptional repression of *dnmt1* and *dnmt3b*, allowing p53 to bind to intron 1 of the *ulbp2* gene, inducing its expression [118]. In multiple myeloma, treatment with doxorubicin or melphalan activated the senescence program and caused DNA-dependent upregulation of the NK ligands PVR and MICA/B, a phenomenon verified in patient samples as well [119], while CDK4/6 inhibition promoted T-cell-mediated clearance of tumor cells [42]. In summary, senescent stromal or cancer cells can induce the expression of immune ligands and secreted factors for enhanced immune clearance, whereas a subset of the SASP can act in the opposite way, leading to immune evasion and survival of malignant cells.

5. Therapeutic elimination of TIS cells

Although activation of senescence limits tumor growth, reversal of this phenotype has been observed. Moreover, persistent presence of TIS is linked to tumor progression and adverse reactions to the therapy mainly because of the SASP. Thus, different strategies have emerged for the elimination of TIS cells, including senolytic approaches that aim to specifically target senescent cells without affecting viability of proliferating cells [16,104,120]. One popular approach is the so-called “one-two punch” where cancer cells are first made vulnerable using a senescence-inducing drug, and then eliminated using a senolytic agent [121,122]. BH3 mimetics are the most known class of senolytic drugs that target anti-apoptotic proteins which are usually upregulated in senescent cells [123,124]. In breast cancer cells, treatment with doxorubicin, paxlitacel or γ -irradiation caused cells to senesce and subsequent treatment with ABT-263 alone or with an MCL-1 inhibitor (for ABT-263 resistant cells) led to their elimination. *In vivo*, sequential treatment with doxorubicin and ABT-263 increased apoptotic tumor cell death and mouse lifespan [125]. Treatment of Estrogen Receptor (ER) positive cells with the ER degrader fulvestrant, palbociclib and ABT-199 (BCL-2 inhibitor) led to decreased cell viability and colony formation and minimal cells growth after removal of the drugs as opposed to therapy with fulvestrant and palbociclib only. In addition, this combinatorial treatment led to increased expression of MHC-I molecules by cancer cells and enhanced immune cell activation *in vivo* [126]. A senolytic that disrupts the senescence-associated interaction between FOXO4 and p53, causing nuclear exclusion of the latter, and ultimately p53-dependent apoptosis was shown to reduce doxorubicin-induced toxicity in mice [80]. In a recent study, the senescence-associated urokinase-type plasminogen activator receptor (uPAR) was efficiently targeted by chimeric antigen receptor (CAR) cytotoxic T cells, and treatment of mice bearing lung adenocarcinomas with MEK and CDK4/6 inhibitors followed by anti-senescence CAR-T treatment led to increased survival [127].

As many tumor cells induced to senesce via chemotherapy develop polyploidy, additional approaches to eliminate senescent cells may rely on targeting the emergent polyploid cells. This can be achieved by targeting common processes occurring in both senescent and polyploid cells, such as targeting their metabolic reprogramming, their increased autophagic flux, their dependence on cell cycle regulators and DNA checkpoints, or via the stabilization of the nuclear lamina to help prevent senescence escape [68,120,128].

6. Conclusion

Cellular senescence is a phenotype that has persisted during evolution due to antagonistic pleiotropy, as it is an important mediator during embryogenesis and wound healing, even though later in life its role can be detrimental. In cancer, it is an important tumor suppressive mechanism that activates immune surveillance and clearance but acts as a double-edged sword by secreting SASP factors that cause inflammation, induce proliferation of neighboring cells and cause immunosuppression or by ultimately escaping this phenotype leading to cancer relapse and metastasis. Therapy-induced senescence is a type of premature senescence caused by genotoxic agents to normal or cancer cells. Research is ongoing on the mechanisms of their induction and maintenance, the role of the SASP in bystander senescence and immune regulation and the development of drugs and immune approaches that will specifically eliminate senescent cells and make a step forward in the battle against cancer and the improvement of life quality in cancer patients.

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Declaration of Competing Interest

MD is a co-founder and advisor of Cleara Biotech. All other authors declare no competing financial interests.

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