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Review Article

Oncogene-induced senescence: a double edged sword in cancer

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Abstract

Oncogene-induced cellular senescence (OIS) is a complex program that is triggered in response to aberrant activation of oncogenic signaling. Initially, OIS was thought to be a barrier to malignant transformation because of its suppression on cell proliferation. Later studies showed that senescence induced by oncogenes can also promote the initiation and development of cancer. The opposing effects of OIS occur through different combinations of downstream effectors as well as the interplay of senescent cells and the microenvironment, such as senescence-associated inflammation. Here, we review the common features and molecular mechanisms underlying OIS and the interaction between senescent cells and the microenvironment. We propose that targeting senescent cells may have a beneficial therapeutic effect during the treatment of cancer.

Keywords: cellular senescence; oncogene; SASP; tumor microenvironment; cancer therapy

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Introduction

Cellular senescence was discovered by Leonard HAYFLICK and Paul MOORHEAD more than five decades ago and was identified as a stable exit from the cell cycle resulting from the limited proliferative capacity of normal human fibroblasts in culture. This particular type of cellular senescence is referred as "replicative senescence" and was demonstrated to be a consequence of shortened telomere length[1-3]. Cellular senescence can be induced by other types of stimuli, such as oncogenic stress. Oncogenic activation is well known as a critical mechanism for the initiation and development of cancer. Although the activation of oncogenes can stimulate cell proliferation, which is recognized as a tumor-promoting event and a necessary step in tumorigenesis in many cancer types, it may act as a genetic stress and cause irreversible growth arrest in cultured cells and tumor tissues[1]. For example, oncogenic mutations in *Ras* have been found to induce cellular senescence in cultured human primary lung fibroblasts IMR90[3]; the hyper-expression of *Ras* in mammary epithelial cells triggered the activation of tumor suppression pathways and irreversible senescent growth arrest *in vivo*[4]. This type of cellular senescence is termed premature senescence, and senescence induced by oncogenes is defined as oncogene-induced senescence (OIS). OIS can also be induced by the activation of other oncogenes, such as *BRAF*, *AKT*, *E2F1* and *cyclin E*, and by the inactivation of tumor suppressor genes, including *PTEN* and *NF1*[5]. The expression level of oncogenes seemed to be important for the induction of OIS, as studies revealed that senescence induced by oncogenic *Ras* only occurred when *Ras* was overexpressed[6].

To date, a number of characteristics displayed by senescent cells have been identified both *in vitro* and *in vivo*, which are summarized in Figure 1. In addition to cell-cycle arrest, senescent cells exhibit increased activity of beta-galactosidase at pH 6.0, the activation of signaling pathways and the secretion of a mixture of growth factors, chemokines and cytokines[7]. These processes reflect the mechanisms that contribute to the induction and maintenance of OIS or accompany the execution of the OIS program. It has been demonstrated that the tumor suppressors p53 and RB are two major intrinsic cellular regulators of OIS, and studies have shown that both proteins actively induce OIS *in vitro* and *in vivo*, but their roles in OIS in human cancer cells have not been fully elucidated[8, 9]. Kinases such as p38 and its downstream substrate PRAK as well as PI3K/AKT/mTOR have been reported to mediate OIS responses[10, 11]. Recently, microRNAs (miRNAs) have been widely found to regulate OIS. For example, miR-

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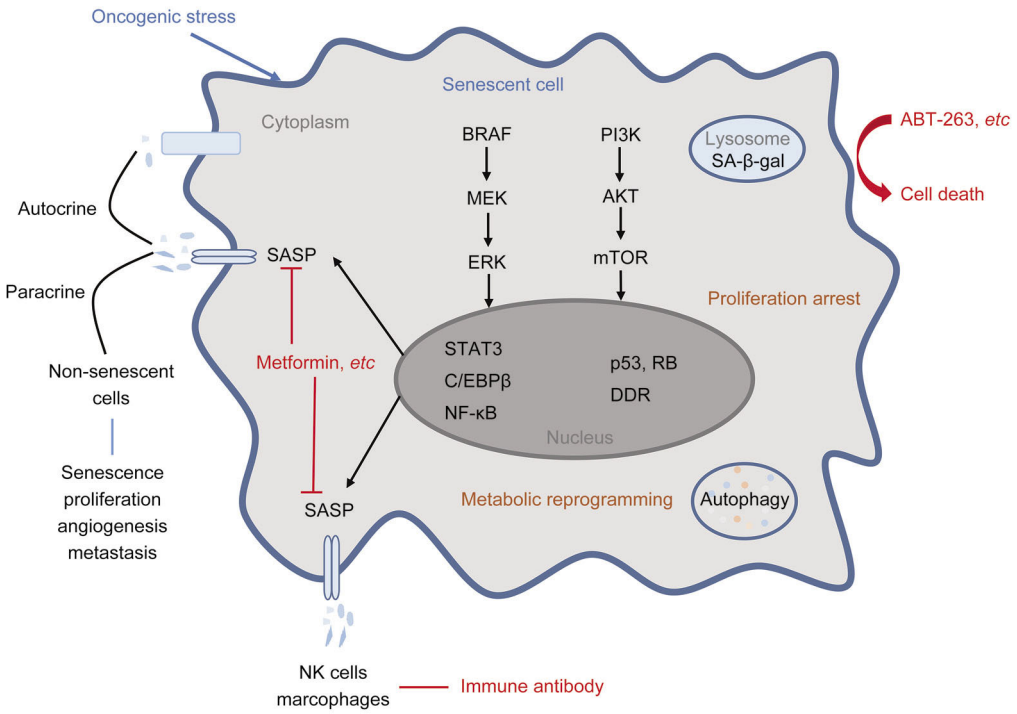

Figure 1. Targeting cellular senescence in cancer. Senescent cells induced by oncogenic stress exhibit proliferation arrest with metabolic reprogramming. Oncogene-induced senescence (OIS) is often accompanied by the activation of signaling pathways such as BRAF/MEK/ERK and PI3K/AKT/mTOR. OIS is usually featured with increased SA-β-gal activation; the accumulation of p53 and/or RB; the activation of DDR and autophagy; and SASP. The senescent phenotype could be different and is dependent on temporal, spatial and genetic contexts. Senescent cells could be eradicated by the induction of apoptosis by pan-BCL inhibitors such as ABT-263 or by the immune surveillance system. In addition, compounds such as metformin that are able to block SASP can eliminate the deleterious effect of cellular senescence.

34a has been reported to mediate *B-RAF*-induced cellular senescence by down-regulating the expression of MYC[12]. In addition, a number of secreted factors have been found to be associated with senescence induced by oncogenes, and these factors exhibit defined but heterogeneous profiles. These mixtures of growth factors, chemokines, cytokines, matrix metalloproteinases and proteases play critical roles in the crosstalk between senescent cells and immune cells or neighboring non-senescent cells[13, 14].

Due to the complex features of senescent cells, senescence can be anti- or pro-tumorigenic under different conditions. OIS is initially thought to be a failsafe program against oncogenic stress because of its ability to restrict the proliferation of abnormal cells[15]. Senescence-associated secretory phenotype (SASP) may also provoke tumor-suppressive responses, which could be beneficial in clearing senescent cells and restraining tumor growth[16]. Subsequent investigations found that senescence may be deleterious and compromise the efficacy of cancer therapy[17]. SASP provokes not only tumor-suppressive but also tumor-promoting responses, which are dependent on the profile of secreted factors. Secreted factors such as vascular endothelial growth factor (VEFG), interleukin-8 (IL-8), interleukin-6 (IL-6) and C-X-C motif chemokine ligand 1 (CXCL1) have been shown to promote tumor progression by stimulating the proliferation of endothelial cells[18], contributing to angiogenesis[19], promoting the invasion of tumor cells[20] or inducing the formation of cancer stem cells[13]. Moreover, factors including CXCL1[21] and ECM-degrading enzymes[22] have been reported to recruit immune cells such as macrophages and NK cells to create an immunosuppressive microenvironment around senescent cells and promote the escape of tumor cells from immune surveillance[23].

RB and p53 are two major regulators in OIS

Despite the complexity of factors involved in OIS, RB and p53 are two main and widely acknowledged regulators, which are responsible for cell-cycle arrest in senescent cells[24-26]. The accumulation of p53 was found in cells undergoing OIS, which could be bypassed when p53 was inactivated. For instance, mice harboring oncogenic Ras^{G12D} developed lung cancer, in which premalignant adenomas expressing p53 were positive for markers of cellular senescence, whereas malignant adenocarcinomas that arose in the absence of p53 were negative for senescence[27, 28]. Senescent cells are often accompanied by the induction of p16, which affects the maintenance of cellular senescence. Cells expressing low levels of p16 would circumvent senescence and resume proliferation[9]. RB exists downstream of p16 and plays a crucial role in cellular senescence. The accumulation of RB was found in senescent cells, and cells would bypass senescence if RB was absent[29]. During cellular senescence, RB preferentially associates with E2F-targeted genes involved in DNA replication and is uniquely required

to repress these genes. Loss of RB leads to inappropriate DNA synthesis upon the triggering of senescence and the disruption of a p21-mediated cell-cycle checkpoint, thereby enabling extensive proliferation and rampant genomic instability[29].

The DNA damage response is an omnipresent mechanism underlying OIS

OIS is associated with the DNA damage checkpoint response (DDR) after a hyper-replicative phase occurred immediately upon activation of oncogenes, which would lead to augmented numbers of active replicons and alterations in DNA replication fork progression. The experimental inactivation of DDR could abrogate OIS and promote cell transformation[30]. OIS was suppressed when ataxia telangiectasia mutated (ATM), a kinase that senses DNA double-strand breaks, was inhibited, which led to increased tumor growth and invasion in mice[31]. A recent study has shown that the degradation of ATM by E3 ubiquitin ligase WD repeat and SOCS box-containing protein 1 (WSB1) contributed to the abrogation of OIS and led to abnormal proliferation and transformation[31]. An analysis of human precancerous lesions revealed that DNA damage and senescence occurred concurrently[32]. ATM and ATR (ataxia telangiectasia and Rad3-related) are able to activate GATA4, which is stabilized in cells undergoing senescence. GATA4 was reported to activate NF-κB to initiate SASP and facilitate senescence, indicating its role downstream of DNA damage[33].

Autophagy is activated in senescent cells

Although proliferation arrest is the main feature of OIS, senescent cells are metabolically active, which is in line with its enlarged morphology. Recently, autophagy was found to be activated during senescence. Autophagy encompasses different routes that cells use to deliver cytoplasmic substrates to lysosomes for degradation, which creates a way for cells to meet the bioenergetic demand when cells have dwindling external or internal resources. Accordingly, autophagy is a protective process against stress and plays key roles in energy homeostasis and quality control of cellular components[34]. A subset of autophagy-related genes is up-regulated during senescence. The overexpression of ULK3 induced autophagy and senescence, while the inhibition of autophagy delayed the OIS-related phenotype, including senescence-associated secretion, suggesting that autophagy and its effectors mediated the acquisition of the senescence phenotype[35]. However, the functional relevance of autophagy and OIS remains unclear. As mentioned previously, the induction of autophagy could reinforce the onset of senescence. Meanwhile, the suppression of autophagy may trigger a stress response, which may facilitate the induction of senescence if cells are sensitive enough to such stress[36]. Thus, autophagy imposes a context-dependent impact on OIS.

SASP enables the communication of senescent cells with the microenvironment

Cells undergoing senescence are metabolically active and secrete multiple factors, including pro-inflammatory cytokines (IL-6 and IL-8), chemokines (monocyte chemoattractant proteins, MCPs and macrophage inflammatory proteins, MIPs), growth factors (transforming growth factor-β, TGF-β and granulocyte–macrophage colony-stimulating factor, GM-CSF) and proteases, and the process is referred to as SASP[37]. The profiles of factors secreted by senescent cells vary depending on circumstances. For example, $BRAF^{V600E}$-induced senescence in different cell lines was associated with diverse secreted factors. The expression of $BRAF^{V600E}$ in human primary foreskin fibroblasts led to the synthesis and secretion of IGFBP7[38], while $BRAF^{V600E}$-induced senescence in human diploid fibroblasts IMR90 was linked specifically to the activation of an inflammatory transcriptome, including IL-6 and IL-8[39]. Factors induced by senescence may paradoxically regulate senescence. IL-6, IGFBP7 and CXCR2 have been demonstrated to be required for OIS, which induced senescence or apoptosis and modulate cell proliferation and migration via autocrine and paracrine[38-40].

SASP is tightly regulated at epigenetic, transcriptional and post-transcriptional levels, contributing to diverse outputs of senescence. A recent study found that OIS triggered a global remodeling of the enhancer landscape with the recruitment of BRD4 to newly activated super-enhancers adjacent to key SASP genes[41]. Transcriptional profiling and functional studies indicated that BRD4 was required for SASP and downstream paracrine signaling. At the transcriptional level, IL-6 or IL-8 is largely regulated by NF-κB and C/EBPβ, while CCL2 or GM-CSF is typically mediated by STAT3[16, 23]. Moreover, SASP factors seem to form a hierarchical network, in which SASP factors including interleukin-1α (IL-1α) and IL-6 appeare to be capable of regulating other secreted factors to transduce and amplify the signal[42]. The transcriptional activity of NF-κB has been demonstrated to be regulated by IL-1α, where the reduction of membrane-bound IL-1α diminished NF-κB activity, resulting in the decreased secretion of inflammatory cytokines, including IL-8[42]. C/EBPβ was reported to act as a transcription factor and cooperate with IL-6 to amplify the activation of the inflammatory network[39].

These factors secreted by senescent cells mainly function by affecting neighboring non-senescent cells and immune cells through paracrine signaling, while senescent cells can also act on themselves in an autocrine manner. TGF-β has been shown to trigger senescence in neighboring proliferating cells in a paracrine manner through a mechanism that generates ROS and DNA damage[43]. Therefore, senescence can be propagated to neighboring cells mediated by SASP and be further reinforced. SASP factors are able to recruit immune cells to clear senescent cells and terminate inflammation. For example, ECM-degrading enzymes secreted by senescent cells have been reported to recruit NK cells to remove senescent cells and thus serve to limit ECM deposition and prevent fibrosis[22].

OIS counteracts cancer progression

Although there are few markers omnipresent in all types of OIS, the stable state of proliferation arrest is a core aspect of the senescent phenotype. Unlike quiescence, senescent growth

arrest is essentially permanent because senescent cells cannot be stimulated to proliferate in most cases. In many tissues, small and inconspicuous neoplastic lesions, where oncogenic mutations and senescence markers have been identified, rarely become overt cancers[27], indicating that senescence caused by aberrant oncogenic activation tends to prevent uncontrolled proliferation through irreversible growth arrest.

Senescence affects tumor development by not only cell-autonomous but also non-cell-autonomous activities, which create spatiotemporally dynamic and context-dependent tissue reactions. Factors such as TGF-β and CCL2 could propagate senescent phenotype to neighboring non-senescent cells, passing oncogenic stress to the microenvironment[7]. Immune cells recruited by senescent cells have been increasingly recognized to play a pivotal role in regulating tumor development. The overexpression of oncogenic *RAS* in mice failed to promote the development of hepatocarcinoma because of senescence-induced immune surveillance, in which CD4+ T cells and macrophages played vital roles in overriding senescent hepatocytes[44]. NK cells could be recruited by CCL2 secreted by senescent cells to assist in clearance of tumor cells, while M1 macrophages could be recruited by CXCL1 to suppress tumor development[21, 45]. However, failure to senescence is usually insufficient for malignant transformation. It appears that senescence poses a formidable but not insurmountable barrier to cancer progression. It has been shown that the activity of wild-type p53 was detrimental to the chemotherapy response in breast cancer patients even if p53 induced senescence in tumors, where the secreted cytokines of senescent cells were able to stimulate cell proliferation and tumor relapse[46].

OIS promotes cancer development

It has been reported that it is very likely for cancer to develop even when OIS occurs. Specifically, in aged organisms, the cell replacement system that involves the clearance of senescent cells and the mobilization of progenitors to re-establish cell numbers may become inefficient or may exhaust the regenerative capacity of progenitor cells, eventually resulting in the accumulation of senescent cells that may aggravate damage and contribute to tumor development[47].

Given the high varieties in SASP and different profiles of SASP in diverse cell types, SASP may provoke either tumor-suppressive or tumor-promoting responses. SASP factors have been shown to promote tumorigenesis by inducing proliferation, survival, angiogenesis and metastasis[16]. For example, primary mouse keratinocytes transiently exposed to SASP exhibited increased expression of markers for stem cell and regenerative capacity *in vivo*[13]. The matrix metalloproteinases (MMPs) secreted by senescent cells would mediate migration and enhance their tumorigenic properties[48]. Factors such as IL-6 and IL-8, which are regulated by mTOR in senescent fibroblasts, were found to promote prostate tumors in mice[42]. SASP may also promote tumorigenesis by its influence on the immune system. For example, CCL2 could recruit M2 macrophages, which creates an immunosuppressive microenvironment and acts as a promoter in tumor progression[49]. CCL2 secreted by senescent hepatocytes has also been reported to recruit immature myeloid cells to promote the development of hepatocellular carcinoma through the inhibition of NK cells. Consistently, SASP was reported to be associated with poor survival and early recurrence in hepatocellular carcinoma[50].

Targeting cellular senescence in cancer

Though senescence induced by oncogenes may block cell proliferation, long-term senescence may result in a favorable microenvironment for tumorigenesis, mainly through SASP, which may promote the proliferation of neighboring non-senescent cells and/or provoke immune escape. Therefore, targeting senescent cells and eliminating the deleterious aspect of senescence may be a potential strategy for cancer therapy. Though the understanding of senescence has been greatly advanced in recent years, the specific targets essential for the induction of senescence remain undefined. As shown in Table 1, the current strategy is to target senescence indirectly via clearing senescent cells or blocking SASP.

It has been reported that clearing senescent cells may be beneficial in alleviating tissue inflammation and organ dysfunction and may reduce cancer risk. For example, pan-BCL inhibitors such as ABT-263/ABT-737 were found to induce apoptosis in senescent cells both *in vitro* and *in vivo* and could selectively eliminate senescent cells. These inhibitors have already been tested with success against small cell lung cancer[51, 52]. Other compounds, including dasatinib, have been shown to override senescence, and dasatinib has been used against acute myeloid and lymphoid leukemia[53, 54]. This strategy could be controversial because the compounds were not specific to induce senescent cells to undergo cell death, and they may function in other ways to restrain tumor growth.

Table 1. Strategies of targeting cellular senescence.

Strategy	Approach		Example	Ref
Elimination of senescent cells	Apoptosis inducer		ABT-263, dasatinib	[51-54]
	Immune system-mediated clearance	Specific antibody	CD44 antibody	[55]
		Specific antibody with cytotoxic agent	DPP4 antibody coupled to cytotoxicity	[56]
SASP attenuation	Targeting SASP induction	NF-κB inhibitors	Glucocorticoids, metformin	[57]
		mTOR inhibitors	Rapamycin	[42]
	Blocking activity of SASP	Inhibitors of secretory factors	Anti-IL-6 receptor antibody, IL-6 inhibitor	[58]

The immune surveillance system could be utilized to eradicate senescent cells as well. For example, antibodies against senescence-specific antigens, such as CD44 in endothelial cells, could induce a direct immune response to eliminate senescent cells and enhance the antitumor effects of cytotoxic drugs[55]. Antibodies that recognize epitopes that are more highly expressed in senescent cells compared to non-senescent cells, coupled to a cytolytic agent, would be helpful to eliminate senescent cells[56].

Senescent cells are thought to contribute to tissue dysfunction largely through chronic inflammation, and several anti-inflammatory drugs have been explored as effective modulators of SASP. Targeting SASP in senescent cells may be a strategy for cancer treatment as well. For example, glucocorticoids, a group of steroid hormones, down-regulated the secretion inflammatory components of SASP through inhibiting the transcriptional activity of NF-κB[57]. Metformin, a commercially anti-diabetic drug, has been reported to prevent the translocation of NF-κB to the nucleus and effectively suppress the induction of SASP[57]. Due to the complicated role of senescence in tumors and its microenvironment, not only the genetic and cellular contexts of senescent cells but also the communication between senescent cells and their microenvironments should be taken into consideration when exploiting senescence in cancer therapy.

Concluding remarks

OIS is a complex process that may play opposite roles in tumor initiation and development depending on temporal, spatial and genetic contexts. Targeting senescent cells may be beneficial for cancer therapy in certain circumstances. Though the understanding of senescence has been greatly advanced in recent years, various senescent responses make it difficult to establish uniform diagnostic criteria for cellular senescence. Currently, a combination of several features of cellular senescence is utilized to detect senescent cells. Further studies are warranted to reveal the essential mechanisms underlying OIS. Given the complexity of OIS, the diversity in the pathological function of senescent cells as well as the dynamic interplay between senescent cells and the microenvironment should be further explored when targeting senescence as a therapeutic option for cancer. In addition, the senescent phenotype of cancer cells may offer potential biomarkers for cancer diagnosis and prognosis. Taken together, great efforts must be made to elucidate the more detailed mechanisms underlying OIS, the interplay between senescent cells and the microenvironment and the roles of OIS in cancer development and therapy.

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