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Inflammatory Signaling and Cellular Senescence

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Abstract

Inflammation is a double-edged sword in the pathogenesis of cancer. Inflammatory responses play a key role in eliminating the potentially cancerous cells. However, inflammatory microenvironment also promotes the development of cancer. Pro-inflammatory cytokines, the key mediators of inflammation, also play a dual role in oncogenesis. While they can promote neoplastic progression, recent studies have revealed an unexpected function of the inflammatory pathways in inhibiting cancer development. These studies demonstrate that cells undergoing senescence, a cellular program serving as a barrier to cancer development, produce increased amount of inflammatory cytokines. These inflammatory cytokines play an essential role in the initiation and maintenance of cellular senescence, and is responsible for triggering an innate immune response that clears the senescent tumor cells in vivo. The purpose of the present review is to discuss the dual roles of the inflammatory cytokines produced by senescent cells in the pathogenesis of cancer, and the signaling pathway mediating their role in cellular senescence.

1. Introduction

The function of the immune system is to protect against foreign substances such as bacteria and viruses and to eliminate endogenous damaged cells. Based on this classic concept of immunosurveillance, immune system should play a key role in preventing tumor initiation and development. Indeed, many studies have demonstrated the existence of cancer immunosurveillance processes that protect the host against the development of primary cancer [1,2]. The adaptive immune system reacts to tumors in a same manner as to foreign pathogens, by stimulating immune cells to recognize tumor-specific antigens and activating the functions of immune effectors, leading to eradication of cancerous cells. However, the effect of immune system on cancer is paradoxical. Substantial evidence shows that inflammation, the major innate immune response to infectious pathogens and to endogenous dangerous cells, can promote the development of many types of cancers. In contrast to the role of cancer immunosurveillance, chronic inflammation provides a microenvironment that promotes cancer development in many cases [3,4]. Immune cells recruited into the tumor microenvironment produce growth factors for epithelial and endothelial cells, inflammatory cytokines and chemokines that enhance cell proliferation and survival and angiogenesis, and immunosuppressive mediators that inhibit cancer immunosurveillance of the host [5,6]. Collectively, these factors facilitate the malignant progression of tumors. The role of inflammation in the initiation of tumors has also been suggested. For example, chronic

inflammation is linked to oxidative stress, which can cause DNA damage and thus contribute to the accumulation of cancer-initiating genetic alternations in cells.

Adding to the complexity of the effect of the immune system on cancer development, recent studies have revealed the involvement of inflammation in cellular senescence, a tumor suppressing mechanism that is equally important as apoptosis in restricting tumor development *in vivo*. These studies show that the gene expression patterns in senescent cells mimic the inflammatory response and wound repair processes. The inflammatory state of cellular senescence again displays dual effects on tumor development. Production of inflammatory cytokines and chemokines is essential for the induction and maintenance of senescence, which prevents premalignant tumor cells from progressing into malignancies, and is responsible for the clearance of the senescent, premalignant tumor cells *in vivo*. Meanwhile, these inflammatory cytokines and chemokines produced by the senescent cells also provide a cancer-promoting microenvironment for their neighboring tumor cells. As a result, the net effect of the inflammatory state of senescence on cancer development will greatly depend on the tissue context, the genetic makeup of the tumor cells as well as the stromal cells, and the extracellular stimuli present in the tumor microenvironment.

2. Cellular senescence

2.1 Cellular senescence and cancer

Cellular senescence is a permanent cell cycle arrest initially described as the terminal phase of primary human cell populations when passaged in cell culture. This type of cellular senescence is thus termed replicative senescence, in reference to the exhaustion of replicative potential of the primary cells cultured *in vitro* as the cause of senescence. In human cells, replicative senescence usually occurs as a result of telomere attrition caused by the failure of the DNA replication machinery to replicate the chromosomal ends during cell division, while in mouse cells with long telomeres, replicative senescence occurs mainly due to suboptimal culture conditions. Permanent cell cycle arrest with phenotypes similar to replicative senescence can also be induced prematurely in both normal and transformed cells by a variety of stress challenges, such as oxidative stress, radiation, activated oncoproteins and others. Unlike replicative senescence, the stress-induced premature senescence is independent of the telomere length or the number of cell divisions.

Cellular senescence is closely associated with cancer development. Premature senescence induced following activation of oncogenes or inactivation of tumor suppressor genes [7] is a potent anti-tumorigenic defense mechanism. It has been well documented that cellular transformation by activated *ras* requires cooperation from ‘immortalizing’ oncogenes that overcome the senescence response, such as those inactivating p53 [8–10]. Recent studies have demonstrated that senescent cells can be detected in early-stage, premalignant lesions of lung, pancreas, skin and prostate in both human cancer patients and mouse tumor models [11–16]. Disruption of senescence by inactivating essential mediators of senescence, such as a histone methyltransferase Suv39h1 and a protein kinase PRAK, accelerates the development of malignant tumors [14,16]. These findings indicate that oncogene-induced senescence occurs *in vivo* and provides a *bona fide* barrier to cancer development. In addition, it has been demonstrated that senescent cells can promote tumor progression in a paracrine fashion. Cells undergoing replicative senescence or oncogene-induced senescence secrete growth factors, inflammatory cytokines and chemokines, and extracellular matrix-degrading proteases that enhance the proliferation, invasion and angiogenesis of nearby premalignant tumor cells [17]. As senescent cells accumulate with age, these observations have provided an explanation to the age-related increase in cancer incidence.

2.2 Characteristics of cellular senescence

Senescence is a form of irreversible proliferative arrest at the G1 phase of cell cycle [18,19]. Senescent cells cannot be stimulated to reenter cell cycle by growth factors. Consistent with the arrest in G1, senescence is accompanied by upregulation of several inhibitors of cell proliferation, including p53 and cyclin-dependent kinase (CDK) inhibitors p16^{INK4A}, p15^{INK4B}, p14/p19^{ARF}, and p21^{WAF1}, decreased cyclin A expression and CDK2 activity [18,20], and silencing of E2F target genes [21]. Senescent fibroblast cells usually display flattened morphology and enlarged cell sizes, with the presence of multiple vacuoles in the cytosol. Multiple markers have been identified that differentiate senescence from other forms of growth arrest such as quiescence [12,22,23]. These markers include senescence-associated β -galactosidase (SA- β -gal) [22], a pH-dependent lysosomal β -galactosidase encoded by the GLB1 gene [24] and p16^{INK4A} and p15^{INK4B}, two small protein inhibitors of CDKs [23]. Senescent cells display a distinct chromatin structure known as senescence-associated heterochromatic foci (SAHF), which may be responsible for the selective silencing of gene expression necessary for the maintenance of the stability of the senescence state [21]. Global transcriptome analysis of senescent cells has revealed that a unique pattern of gene expression that differs from proliferating cells and cells undergoing quiescence, contact inhibition or DNA damage-induced growth arrest. In addition to the cell cycle regulatory genes, the expression of others, including inflammation and stress-associated genes, DNA damage checkpoint genes, genes encoding extracellular matrix proteins and extracellular matrix-degrading enzymes, cytoskeletal genes, and metabolic genes, is in general altered during replicative and premature senescence, although expression pattern of these genes is highly cell type-specific [25–31].

2.3 Signaling pathways mediating cellular senescence

Cellular senescence is almost invariably enforced by the p53/p21^{WAF1} and/or p16^{INK4A}/Rb tumor suppressor pathways. Senescence is usually accompanied by the induction of expression and/or activity of p16^{INK4A} and p53 [18,32]. p53 in turn induces the expression of its transcriptional target p21^{WAF1}, which, together with p16^{INK4A}, inhibits the activity of CDKs that phosphorylates Rb at the G1/S transition. This leads to accumulation of the hypophosphorylated, active form of Rb that inhibits the ability of the E2F transcription factors to transcribe genes necessary for proliferation [33], thereby resulting in cell cycle arrest and other phenotypes of senescence.

Although the signaling pathways upstream of p53 and p16^{INK4A} vary among different types of senescence, recent studies suggest the DNA damage response as a common mediator [17]. Telomere attrition leads to formation of DNA damage sites on telomeres [34–36]. Activated oncogenes such as *ras* induces DNA damage caused by DNA hyper-replication resulted from the mitogenic signals transduced by these oncogenes [37,38]. Senescence induced by some stress signals is accompanied by increased intracellular levels of reactive oxygen species (ROS), which again are capable of causing DNA damage [39–41]. The DNA damages generated during senescence in the above cases trigger a DNA damage checkpoint response involving classical DNA damage checkpoint proteins, such as ATM, Chk2, and p53, and sometime also p16^{INK4A}, which play an essential role in the initiation and maintenance of senescence. Moreover, multiple studies have also suggested a common role of the p38 MAPK pathway in cellular senescence [42]. Activation of p38 is essential for replicative senescence as well premature senescence induced by oncogenes, oxidative stress and suboptimal culture conditions [43–46]. In the case of oncogenic *ras*-induced senescence, the MKK3/6-p38 pathway is induced as a result of persistent activation of the Raf-MEK-ERK pathway [43, 44], and triggers senescence through a p38 downstream substrate kinase p38-regulated/activated kinase (PRAK) that in turn stimulates the activity of p53 through phosphorylation [16]. Activated p38 also induces the mRNA level of another key senescence effector p16^{INK4A} though an unknown mechanism [43]. Since the p38 pathway can be activated by

DNA damage [42], it is likely that p38 activation is a result of DNA damage generated during senescence induced by various signals.

3. Inflammation and cellular senescence

3.1 The inflammatory state of senescent cells

The connection between inflammation and cellular senescence was initially suggested by studies on the gene expression profiles of senescent cells. These studies demonstrate that senescence is associated with gene expression patterns similar to those observed in inflammatory responses and wound healing processes. Increased expression of inflammation-associated genes including the chemokines monocyte chemoattractant protein-1 (MCP-1) and Gro- α , cytokines IL-15 and IL-1 β , Toll-like receptor 4 (TLR4) and intercellular adhesion molecule-1 (ICAM-1), was observed in replicatively senescent human dermal fibroblasts (such as BJ foreskin fibroblast cells, and C4 and MA fibroblast cells derived from the hand and ankle respectively of the same donor) [25,30]. However, these changes were not detected in senescent retinal pigment epithelial cells and vascular endothelial cells, suggesting that the senescence-associated inflammatory response is cell type-specific. Upregulation of the inflammatory regulator genes is not restricted to senescent fibroblasts, activated human hepatic stellate cells (HSCs) undergoing replicative senescence also showed higher expression of inflammation- and stress-associated genes as compared to early passage HSCs or HSCs immortalized by the catalytic subunit of telomerase (hTERT) [27]. In addition to replicative senescence, the induction of inflammatory network is also linked to premature senescence induced by oncogenes. Increased expression of the inflammatory regulators has been observed in primary human diploid fibroblasts induced to undergo senescence by oncogenic ras (*Ha-rasV12*) [28] or *BRAF* (*BRAF^{E600}*) [47], and in senescent human melanocytes expressing *BRAF^{E600}* [47]. Moreover, introduction of oncogenic *ras* into vascular smooth muscle cell from arteries also induced premature senescence accompanied by enhanced expression of proinflammatory cytokines and chemokines [48]. Taken together, these findings demonstrate that both replicative senescence and oncogene-induced senescence mimic the inflammatory responses in cells of multiple origins.

3.2. Inflammatory response as a mediator of cellular senescence

Although the production of inflammatory regulators like IL-6 and IL-8 by senescent cells had been known for quite a while, it was an unexpected recent finding that these immune mediators play an essential role in the initiation and maintenance of cellular senescence. By using a combination of gene expression profiling and RNAi analyses, Kuilman et al. found that oncogene-induced senescence was relayed by an interleukin-dependent inflammatory network [47]. They conducted an unbiased gene ontology analysis of the microarray data, which revealed that oncogenic *BRAF^{E600}*-induced premature senescence in human fibroblasts was specifically associated with upregulation of the expression levels of inflammatory cytokines and chemokines, such as IL-6. The increased expression of these genes was also observed in primary melanocytes, the cell type in which *BRAF^{E600}* plays a major role in the induction of melanoma. More importantly, IL-6 is required for the execution of oncogene-induced senescence because knockdown of IL-6 or IL-6R prevented senescence induction by *BRAF^{E600}*. Although IL-6 signaling alone was not sufficient to induce senescence, it enhanced senescence induction by *BRAF^{E600}*, suggesting that IL-6 is a rate-limiting component of the senescence-inducing pathway. Interestingly, while IL-6R is required for senescence induction, treatment with neutralizing antibodies against IL-6 failed to block senescence. This indicates that IL-6 acts in an autocrine fashion to mediate oncogene-induced senescence. On the other hand, the pool of IL-6 secreted to the extracellular compartment by the senescent cells had promitogenic activity, as it enhanced proliferation of tumor cells in a paracrine fashion. Combined with previous reports that IL-6 secreted by Ras-expressing cells promotes

angiogenesis and tumor growth [49], these findings demonstrate that the autocrine and paracrine signaling pathways of IL-6 produced by senescent cells have differential roles in tumorigenesis.

Although the exact signaling pathway responsible for the function of IL-6 in senescence is unknown, the increased IL-6 expression is mediated by C/EBP β , a transcription factor that is induced and recruited to IL-6 the promoter upon senescence induction [47,50]. At least one of the downstream (most likely indirect) targets of IL-6 is the CDK inhibitor p15^{INK4B}, as silencing of IL-6 abolishes its induction by *BRAF*^{E600}. Furthermore, IL-6 seems to be the central regulator of the inflammatory network that mediates oncogene-induced senescence. Depletion of IL-6 by shRNA abolishes the induction of other inflammatory cytokines and chemokines, including IL-8, a chemoattractant for neutrophils at inflammation sites. At least one of these IL-6-dependent cytokines and chemokines, IL-8, is also regulated by C/EBP β and is essential for *BRAF*^{E600}-induced senescence. Furthermore, in human colon adenomas, increased IL-8 expression was detected in areas displaying features of senescence (p16^{INK4A}-positive and Ki-67-negative), suggesting that induction of the inflammation network contributes to senescence in vivo.

Besides oncogene-induced senescence, the inflammatory mediators also play a key role in replicative senescence. In a genetic screen designed to search for genes essential for replicative senescence, a small hairpin RNA (shRNA) targeting the CXCR2 chemokines receptor was identified as being capable of delaying replicative senescence and extending the life span of primary human fibroblasts [51]. Further studies demonstrated that silencing of CXCR2 alleviated not only replicative senescence, but also oncogene-induced senescence, while ectopic expression of CXCR1 or CXCR2 led to p53-dependent premature senescence. The expression level of CXCR2 is increased during both replicative senescence and oncogene-induced senescence. This was accompanied by the concurrent upregulation of the levels of all CXCR2 ligands including IL-8, and other proinflammatory cytokines, in a NF- κ B-, C/EBP β -, and possibly also p38 MAPK-dependent fashion. The induced IL-8, a CXCR2 ligand, is responsible for the activation of CXCR2 during senescence. In addition, IL-8 and GRO α , another CXCR2 ligand, also play an important role in cellular senescence, as ectopic expression of IL-8 or GRO α reduced cell proliferation, while shRNA targeting IL-8 or GRO α inhibited senescence. Interestingly, unlike IL-6 [47], neutralizing antibodies against IL-8 or GRO α also alleviated senescence, suggesting that secreted CXCR2 ligands also contribute to senescence. These findings indicate that the activation of chemokine signaling via the CXCR receptors plays an essential role in execution of cellular senescence. The expression of CXCR2 and its ligands, as well as IL-6 and its receptor, was found increased in carcinogen-induced benign mouse skin papillomas containing senescent cells. In human prostate tissues, epithelial cells with increased CXCR2 and CXCR1 expression were detected in premalignant intraepithelial neoplasia (PIN) lesions enriched in senescent cells, but not in normal prostate glands or malignant prostate adenocarcinoma (PCa). In addition, a CXCR2 mutant defective in chemokine signaling was identified from a lung carcinoma cell line. Unlike wild type CXCR2, this mutant failed to induce premature senescence and alleviated oncogene-induced senescence, when ectopically expressed primary fibroblasts. These suggest that CXCR2-mediated chemokine signaling contributes to senescence induction during tumorigenesis in vivo, and that mutations of the components in the CXCR2 pathway may compromise the tumor-suppressive senescence response and promote cancer progression.

Collectively, the above studies have demonstrated an inflammatory cytokine-signaling pathway that mediates the induction of cellular senescence (Fig. 1). The senescence stimuli initially activate C/EBP β , NF- κ B, and p38 through mechanisms yet to be identified, leading to increased expression of IL-6. IL-6 in turn induces the expression levels of other inflammatory cytokines and chemokines including those binding to the CXCR2 receptor. The senescence signals also induce the expression level of CXCR2, which is activated in the presence of the

increased amount of CXCR2 ligands. The induced CXCR2 activates the senescence effectors, such as p15^{INK4B}, p16^{INK4A} and the p53/p21^{WAF1} circuit, triggering cellular senescence. This inflammatory pathway crucial for cellular senescence involves a self-amplifying network of inflammatory mediators that are usually regulated by each other and at multiple levels. Within this pathway, C/EBP β and IL-6 form a positive feedback loop, as C/EBP β mediates the increased expression of IL-6, and the induction of C/EBP β requires IL-6. Moreover, C/EBP β directly stimulates the transcription of not only IL-6, but also the cytokines that are induced by IL-6. Furthermore, while the function of IL-6 in the execution of senescence is mainly mediated by an autocrine effect, a paracrine pathway at least partly contributes to the role of IL-8 and other CXCR2 ligands in senescence.

3.3. Inflammatory response and clearance of senescent tumor cells

Both apoptosis and cellular senescence are considered as tumor suppressing mechanisms in vivo. However, unlike apoptosis, senescence is a cytostatic program in which the arrested tumor cells remain alive although they do not proliferate. The fate of senescent cells in vivo had thus been unclear. Using a mouse liver carcinoma model, a recent study demonstrated that in vivo, senescent tumor cells are cleared by an innate immune response triggered by the inflammatory cytokines secreted by the senescent cells [52]. In this study, a chimeric liver cancer mouse model was created in which the tumor cells contained a repressible p53 shRNA. Upon suppression of p53 shRNA, p53 activity was restored, leading to irreversible tumor regression mainly achieved through a senescence program. While these tumor cells entered senescence and remained arrested upon p53 reactivation in vitro, p53 activation and subsequent senescence induction in tumor cells in vivo led to a progressive infiltration of host leukocytes (neutrophils, macrophages and natural killer cells) into the tumor tissues. This was accompanied by increased production of inflammatory cytokines known to attract these leukocytes, and adhesion molecules including ICAM1 and VCAM1, in liver tumors following p53 reactivation. Moreover, suppression of macrophages, neutrophils or natural killer cells delayed tumor regression caused by p53 reactivation, demonstrating an essential role of the host innate immune cells in the clearance of senescent tumors. These findings suggest that increased production of inflammatory regulators in senescent tumor cells facilitates the recruitment of host innate immune cells, leading to the destruction of tumor cells and tumor clearance (Fig. 1).

3.4. Inflammatory responses of senescent cells as a promoter of tumor development

3.4.1. The pro-tumorigenic effect of senescent cells—While cellular senescence is tumor-suppressing mechanism when acting in a cell autonomous fashion, senescent human fibroblasts can stimulate nearby premalignant and malignant epithelial cells to proliferate in culture and to form tumors in mice [53,54]. These senescent stromal cells enhance tumor development at multiple levels, including tumor cell proliferation, contact-independent growth, tumor angiogenesis, and tumor cell invasion and metastasis [17,55]. This pro-tumorigenic effect is at least partly mediated by factors secreted by senescent cells, and exists in cells undergoing different types of senescence. Recently studies have indicated that these tumor-promoting factors produced by senescent cells include inflammatory cytokines [56], in addition to growth factors [57,58], angiogenesis factors [59] and matrix-degrading proteinases [57,60, 61].

3.4.2. The pro-tumorigenic effect of inflammatory cytokines produced by senescent cells—Many of the inflammatory mediators produced by senescent cells are known to enhance tumor angiogenesis and tumor cell proliferation, invasion and metastasis. IL-6 stimulates the proliferation of tumor cells, protects tumor cells from apoptosis, and promotes tumor metastasis and angiogenesis by inducing the expression of adhesion molecules and angiogenic factors [62–66]. The level of circulating IL-6 is often found increased in cancer

patients [67]. IL-8 is a potent stimulator of endothelial cell migration and angiogenesis, tumor growth and survival, and tumor metastasis [68,69]. IL-1 also promotes angiogenesis, tumor growth and metastasis in experimental model, and inhibition of IL-1 signaling reduces tumor development [70]. Increased production of IL-1 due to polymorphisms in the IL-1 gene in some individuals is associated with increased risks of cancer development and poor prognosis [71–73]. In addition to these secreted inflammatory cytokines, senescent cells also overexpress cyclooxygenase (COX)-2, a key enzyme in the synthesis of inflammatory mediator prostaglandins (PGs) [27,30]. Through the production of PGs, COX-2 promotes tumorigenesis by inhibiting apoptosis, stimulating cell proliferation and angiogenesis, and suppressing immunosurveillance [4,74]. Although many of these studies investigated the roles of the inflammatory cytokines produced by immune cells recruited to the microenvironment of tumors, these same factors secreted by senescent stromal cells should in principle have a similar effect on nearby tumors (Fig. 1).

4. Perspective

It has been well established that inflammation plays a crucial role in the pathogenesis of cancer. Mounting evidence has indicated that tumors can take advantage of some of the molecular apparatus of inflammation for their growth and metastasis. Inflammatory cells are recruited to and activated in the microenvironment of a developing tumor, where they promote neoplastic progression of the tumor by producing a myriad of soluble growth factors, cytokines and chemokines, as well as various types of extracellular matrix-degrading enzymes, including matrix metalloproteinases (MMPs). These secreted factors contribute to multiple aspects of cancer development, including angiogenesis, tumor cell proliferation and survival, and tumor invasion and metastasis. Interesting, this cancer-promoting, inflammatory gene expression network is shared by cells undergoing replicative senescence or oncogene-induced senescence. These findings suggest that like tumor-associated immune cells, senescent stromal cells can also promote the progression of tumors within the microenvironment. Since senescent cells accumulate with age, the pro-tumorigenic function of the senescent stromal cells may have provided an explanation to the age-dependent increased in cancer incidence. Moreover, while oncogene-induced senescence is a tumor-suppressing mechanism when operating cell-autonomously, it creates a microenvironment favoring the progression of nearby premalignant lesions. This “paracrine” effect adds to the diversity of the routes by which an oncogene induces cancer in vivo.

In contrast to their tumorigenic activity, the inflammatory cytokines produced by senescent cells also plays an essential role in the induction and maintenance of cellular senescence itself, and is responsible for tumor clearance by recruiting immune cells to tumors containing senescent cells. Since senescence is a tumor-suppressing program, these findings suggest that the inflammatory cytokines also mediate a cell-autonomous pathway that inhibits tumor development. Thus, inflammation likely plays a dual role in the pathogenesis of cancer. In vivo, cells with increased expression of inflammatory cytokines have been shown to co-localized with senescent, growth-arrested cells in premalignant lesions from mouse cancer models or human cancer patients, raising a possibility that the inflammatory network may be responsible for senescence induction in vivo. However, these observations are correlative, and the causative role of inflammation in senescence in vivo has yet to be established.

These dual roles of senescence-associated inflammation in cancer may be distinguished by their temporal and spatial differences. While tumor promotion by inflammatory cytokines are achieved through a paracrine effect after being secreted into the tumor microenvironment, the function of these cytokines in cellular senescence is cell autonomous, and is mainly mediated by an autocrine pathway (Fig. 1). Furthermore, the inflammatory cytokines produced by senescent cells or immune cells enhance the progression of already initiated tumors present in

the microenvironment. On the other hand, cellular senescence, especially oncogene-induced senescence, serves as an initial barrier to tumorigenesis by suppressing tumor development at early, initiation stages [11,42]. Thus, by mediating senescence, inflammatory cytokines may suppress these initial stages of tumorigenesis. Therefore, the tumor-suppressing function of senescence-associated inflammation may act earlier on in cancer development, as compared to its tumor-promoting function.

The dual roles of inflammation in cancer development have a significant implication concerning the design of anti-cancer drugs. Several anti-inflammatory medications have been considered for cancer treatments. A challenging issue with respect to these approaches is how to therapeutically manipulate the tumor-suppressing and tumor-promoting properties of inflammatory responses. For example, an anti-inflammation therapy targeting the pro-tumorigenic activity of inflammation could also inhibit oncogene-induced inflammatory responses essential for senescence induction and prevention of tumor formation, and the host immunosurveillance program that helps eradicating established cancer. Although the initial studies have implicated C/EBP β and NF- κ B as potential transcriptional activators of inflammatory cytokines in senescent cells, the exact upstream pathways responsible for the induction of these cytokines and the downstream pathways mediating their functions in senescence are currently unknown. A better understanding the molecular mechanisms and signaling pathways that mediate the roles of inflammation in cellular senescence and in tumor promotion will provide valuable information for the design of optimal cancer therapies targeting inflammation.

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Fig. 1.

Signaling pathways mediating the dual roles of senescence-associated inflammatory cytokines in cancer development. The senescence stimuli, such as telomere attrition, activated oncogenes, DNA damage, initially activate C/EBPβ, NF-κB, and p38 through mechanisms yet to be identified, leading to increased expression of IL-6. IL-6 in turn induces the expression levels of other inflammatory cytokines and chemokines including those binding to the CXCR2 receptor. The senescence signals also induce the expression level of CXCR2, which is activated in the presence of the increased amount of CXCR2 ligands. The induced CXCR2 activates the senescence effectors, such as p15^{INK4B}, p16^{INK4A} and the p53/p21^{WAF1} circuit, triggering cellular senescence. Within the pathway, C/EBPβ and IL-6 form a positive feedback loop, as C/EBPβ mediates the increased expression of IL-6, and the induction of C/EBPβ requires IL-6. Moreover, C/EBPβ directly stimulates the transcription of not only IL-6, but also the cytokines that are induced by IL-6. While the function of IL-6 in the execution of senescence is mainly mediated by an autocrine effect, a paracrine pathway at least partly contributes to the role of IL-8 and other CXCR2 ligands in senescence. The inflammatory cytokines secreted to the extracellular compartment by senescent cells also have paracrine functions. They mediate the clearance of tumors by recruiting host immune cells to tumor tissues. In addition, the inflammatory cytokines provide a cancer-promoting microenvironment for nearby tumors by enhancing angiogenesis, tumor cell proliferation and survival, and tumor invasion and metastasis.