Cancer-associated fibroblasts under therapy-induced senescence in the tumor microenvironment (Review)

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Abstract. Current cancer treatments target tumor cells; however, the tumor microenvironment (TME) induces therapeutic resistance, tumor development and metastasis, thus rendering these treatments ineffective. Research on the TME has therefore concentrated on nonmalignant cells. Cancer-associated fibroblasts (CAFs) are a major TME component, which contribute to cancer progression due to their diverse origins, phenotypes and functions, including cancer cell invasion and migration, extracellular matrix remodeling, tumor metabolism modulation and therapeutic resistance. Standard cancer treatment typically exacerbates the senescence-associated secretory phenotype (SASP) of senescent cancer cells and nonmalignant cells that actively leak proinflammatory signals in the TME. Therapy-induced senescence may impair cancer cell activity and compromise treatment responsiveness. CAFs and SASP are well-studied in the formation and progression of cancer. The present review discusses the current data on CAF senescence caused by anticancer treatment and assesses how senescence-like CAFs affect tumor formation. The development of senolytic medication for aging stromal cells is also highlighted. Combining cancer therapies with senolytics may boost therapeutic effects and provide novel possibilities for research.

Contents

1. Introduction

The tumor microenvironment (TME), which consists primarily of the extracellular matrix (ECM), is crucial to various aspects of tumor progression, such as tumorigenesis, metastasis, relapse and treatment resistance, making it a potential target for cancer therapies (1,2). The TME is a complex system comprising a range of cellular and noncellular elements, and cancer-associated fibroblasts (CAFs), which are highly abundant in the tumor stroma and exhibit potent regulatory effects on tumor growth (3,4). The induction of cell senescence through traditional cancer treatments is one of the most notable mechanisms of tumor suppression. However, in cancer, the process of therapy-induced senescence (TIS) is a 'double-edged sword' (5). Despite its indispensable role in combating tumor growth by halting cancer cell division, the chronic accumulation of senescent cells can conceivably promote tumor development (6). Specifically, secretion of the senescence-associated secretory phenotype (SASP) (7), which is induced by TIS, can significantly affect the TME through autocrine and paracrine effects (8).

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Abbreviations: TIS, therapy-induced senescence; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; SASP, senescence-associated secretory phenotype; EMT, epithelial-mesenchymal transition; TGF-β, transforming growth factor β; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; DDR, DNA damage response; HGF, hepatocyte growth factor; SDF, stromal cell-derived factor

Key words: CAFs, TME, cancer, TIS, therapeutic resistance

The aim of the present review was to provide an overview of the most recent research regarding the biological tumor-promoting functions of CAFs. Additionally, this review aimed to emphasize the antitumorigenic properties of senescence-like CAFs within the TME, which are induced by anticancer therapies. Furthermore, a comprehensive overview of the existing senolytic therapies, and their potential advantages in the context of cancer treatment, is provided.

2. Origins, activation and markers of CAFs

Origin of CAFs. Previous studies have highlighted the complexity and diversity of CAFs, one of the diverse components of the tumor stroma, which could be due to their multiple cellular origins and the emergence of various CAF subpopulations (9,10). While the exact origin of CAFs remains unclear, they can be produced through various means. During tumorigenesis, remnant local fibroblasts in the surrounding tissues can undergo gene expression and phenotype changes in response to tumor driver stimuli. For example, 'quiescent' stellate cells in the liver and pancreas, which are the resident fibroblasts in these tissues, can be activated by inflammatory stimuli released by tumors to acquire a myofibroblast-like CAF phenotype (11-13). In addition, CAFs can be recruited from remotely circulating cell populations. One such precursor of CAFs is bone marrow mesenchymal stem cells, which is the most well-studied cell population among the known sources of CAFs (14,15). Moreover, nonfibroblastic lineages that are in close proximity to tumor cells, such as endothelial or epithelial cells, can undergo transdifferentiation into CAFs through endothelial-mesenchymal or epithelial-mesenchymal transition (EMT), respectively. These cells exhibit CAF-like gene expression and represent another source of heterogeneity for the population of CAFs (16,17). Furthermore, transdifferentiation from other uncommon CAF precursor cells, such as adipocytes and pericytes, has been observed under limited conditions (18,19) (Fig. 1).

Activation of CAFs. Cancer progression relies heavily on tumor stromal support to maintain continuous tumor growth and metastasis (20,21). Despite the presence of normal fibroblasts in the matrix surrounding the tumor, they do not hinder cancer cell invasion and metastasis (22). Hence, it becomes essential for cancer cells to transform normal fibroblasts into tumor-promoting CAFs, which are recruited and activated by various tumor-derived signals and specific stimuli in the TME, such as hypoxia and oxidative stress damage (23,24). Among these, transforming growth factor β (TGF-β), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) play crucial roles as biochemical mediators in CAFs (25). It has been indicated that TGF-β has a strong interaction with ECM components in tissues and is an essential cytokine that activates the cancer stroma (26). TGF-β is typically activated locally, and as a result, CAFs produce TGF-β locally in response to its secretion by cancer cells in the surrounding area. This triggers a response in CAFs, enhancing their potential to produce tumor-promoting factors (27,28). PDGF is another growth factor secreted by tumor cells that is closely linked to cancer progression (29). Cellular processes, such as chemotaxis, cell proliferation, division and angiogenesis, are some of the numerous biological processes affected by PDGF, and overexpression of PDGF and its receptors in tumors is a common occurrence. However, most tumor cells do not express PDGF receptors. Rather, PDGF levels are upregulated, implying that PDGF mainly promotes tumor progression through paracrine signaling from other cells, such as fibroblasts and endothelial cells (30,31). Unlike the TGF-β-induced ECM over-deposition phenotype, PDGF mainly enhances fibroblast recruitment and proliferation (32). FGF2 was initially known as a 'basic fibroblast growth factor' that promotes cell differentiation and proliferation between epithelial and mesenchymal cells through autocrine and paracrine processes. Further research has revealed that FGF2 stimulates the activation of normal fibroblasts *in vivo*, conferring their ability to promote metastasis (33). Furthermore, FGF2 can act synergistically with PDGF to promote tumor angiogenesis and metastasis (34).

Markers of CAFs. CAF populations are highly heterogeneous, with differences across various tumor types and cell sources. However, unlike other cell lineages, CAFs do not express specific biomarkers, posing a challenge to their comprehensive characterization. Representative CAF markers have been established, including fibroblast activation protein, PDGF receptor-α/β, α-smooth muscle actin, fibroblast-specific protein 1/S100A4, vimentin, podoplanin, periostin and type-I collagen (35,36). Nevertheless, while these markers are commonly used to identify CAF phenotypic features, none of them offer specificity to CAFs, and the expression of these markers can also be observed in healthy tissues and other cell types. Table I (37-54) lists some typical CAF markers used in cancer studies.

3. The function of CAFs in metastasis

Tumor metastasis is frequently associated with an unfavorable prognosis for patients (55). CAFs are known to be important in tumor development and resistance to cancer therapy; therefore, the functions of CAFs should be closely examined in relation to tumor metastasis. The modulatory effects of CAFs on tumor progression have been well documented in the TME, where they promote tumor progression and metastasis through various mechanisms, including ECM modification, EMT regulation in cancer cells and the release of cytokines that support tumor growth.

CAF-mediated ECM remodeling. ECM remodeling is a vital physiological process for maintaining tissue homeostasis that occurs throughout body development, regeneration and wound healing (56,57). Fibroblasts, found in both healthy and tumor tissues, make a critical difference in producing ECM components and remodeling enzymes in the interstitial space. Tumor-derived factors activate fibroblasts, transforming them into CAFs, which facilitate communication between the tumor and its surrounding stroma. CAFs are responsible for ECM remodeling in distant organs, promoting tumor invasion and metastasis, and can create pathways within the ECM by degrading matrix proteins, allowing cancer cells to penetrate the basement membrane and enter the surrounding tissues, ultimately metastasizing to distant locations (58). This ECM

Table I. Commonly used markers of CAFs.

Marker	Description	Expression in other cells	(Refs.)
FAP	A 170-kDa melanoma membrane-bound gelatinase, serine integral membrane protease	Macrophages	(37,38)
PDGFR-α/β	Cell-surface receptor for homodimeric PDGFB and PDGFD, and for heterodimers formed by PDGFA and PDGFB, tyrosine-protein kinase	Vascular smooth muscle cells, pericytes	(39-42)
α-SMA	Intermediate-filament-associated protein, most highly conserved globular protein	Smooth muscle cells, pericytes, myoepithelial cells	(43-44)
FSP1/S100A4	A member of the calcium-binding protein family, a marker of quiescent fibroblasts	Cancer cells	(45)
Vimentin	Class-III intermediate filament protein, widely expressed in fibroblasts	Endothelial cells, myoepithelial cells and neurons	(46-48)
PDPN	Membrane glycoprotein, extensively O-glycosylated	Endothelial cells	(49)
Tenascin C	Extracellular matrix protein, a marker of myofibroblasts	Cancer cells, endothelial cells	(50,51)
POSTN	Extracellular matrix protein, associated with cancer stem cell maintenance and metastasis	Cancer cells, mesenchymal stem cells	(52,53)
COL1	A member of group I collagen (fibrillar forming collagen), not exclusive to fibroblasts	Cancer cells, endothelial cells	(54)

α-SMA, α-smooth muscle actin; COL, type-I collagen; FAP, fibroblast activation protein; PDGFR, platelet-derived growth factor receptor; FSP1, fibroblast-specific protein 1; PDPN, podoplanin; POSTN, periostin.

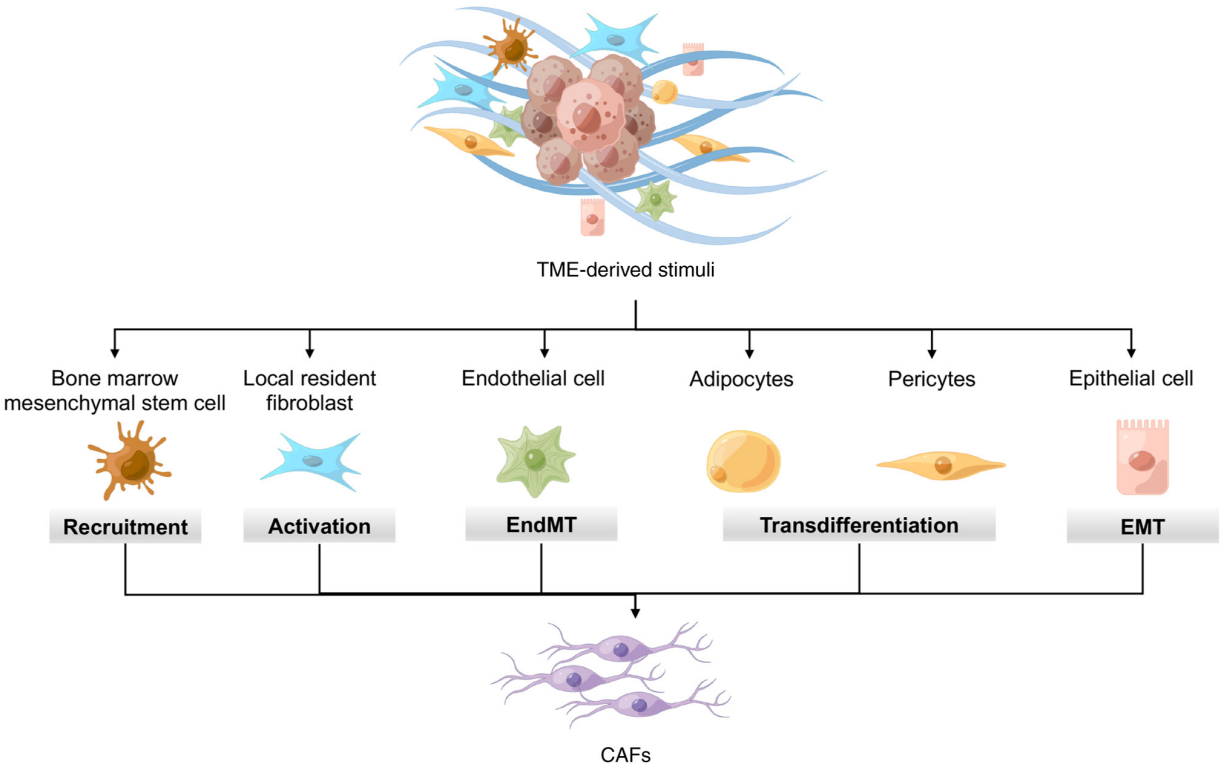

Figure 1. Potential cellular sources of CAFs. In the TME, CAFs comprise a complex cell type. The primary cells that can be activated to produce CAFs are local fibroblasts. Other sources of CAFs have also been proposed, such as epithelial cells (via EMT), endothelial cells (through EndMT), bone marrow-derived mesenchymal stem cells (by recruitment), and adipocytes and pericytes (through transdifferentiation). CAFs, cancer-associated fibroblasts; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition; TME, tumor microenvironment.

remodeling process, facilitated by ECM-degrading enzymes such as rho-associated kinase and matrix metalloproteinases, serves an important role in driving malignant cell invasion and metastasis (59-61).

Role of CAF in EMT and migration. In both embryogenesis and tumor metastasis, the involvement of fibroblasts in promoting EMT is crucial. Generally, cells with a mesenchymal phenotype are more prone to invasion (62). However, carcinomas typically retain the epithelial characteristics that limit their invasive potential. Therefore, cancer cells rely on nonmalignant stromal cell types, with CAFs being the most ideal matrix partners, to facilitate invasion and metastasis. Hybrid EMT, in which malignant cells exhibit a combination of mesenchymal and epithelial characteristics, strongly promotes metastasis (17,63-65). The interaction between malignant cells and CAFs is mediated by cytokines, which is vital for EMT. In recent years, extensive research has been conducted on the CAF-secreted factors involved in EMT in various types of cancer. Among these factors, TGF-β, released by CAFs, has been extensively studied. In advanced cancer, TGF-β enhances the migratory and invasive capabilities of cancer cells by inducing a mesenchymal phenotype. For example, CAFs can activate homeobox transcript antisense intergenic RNA (HOTAIR) transcription through the secretion of TGF-β1, and SMAD2/3/4 can directly bind to the HOTAIR promoter site to increase the ability of breast cancer cells to metastasize (66). Other signaling pathways that drive cancer cells to acquire mesenchymal phenotypes, such as Janus kinase/signal transducer and activator of transcription proteins (JAK/STAT), Wnt/β-catenin, MAPK and PI3K/Akt, can be triggered by CAF-released cytokines, growth factors and chemokines, such as interleukin-6 (67), hepatocyte growth factor (68) and stromal cell-derived factor-1 (69).

Role of CAFs-derived exosomes in cancer progression. As previously mentioned, activated CAFs secrete various messengers that can induce remodeling of the ECM or EMT in malignant cells to facilitate tumor development and progression. In the present section, the ways in which CAF-derived exosomes promote metastasis was focused on. Exosomes, a type of extracellular vesicle, have emerged as novel messengers in intercellular communication; notably, they deliver proteins, DNA and RNA (70). Several studies have identified exosomes secreted by CAFs as key players in the crosstalk between tumors and CAFs, as well as in cancer cell invasion. For example, in gemcitabine-treated human pancreatic ductal adenocarcinoma CAFs, the expression levels of Snail and microRNA (miR)-146a were revealed to be increased in exosomes, and this enhanced cell proliferation and chemoresistance (71). In gastric carcinoma, exosomal miR-522 derived from CAFs was shown to inhibit ferroptosis by suppressing arachidonate lipoxygenase 15 and reducing lipid reactive oxygen species accumulation, resulting in chemoresistance and tumor progression (72) (Fig. 2).

4. Senescence-like CAFs in tumor progression

Cellular senescence. Cellular aging is a response to cellular stress caused by molecular damage. Common triggers of senescence include replicative exhaustion (replicative senescence), hyperactivation of oncogenes (oncogene-induced senescence), and persistent damage to DNA and chromatin structures (73). Cellular senescence is regarded as a vital intrinsic tumor-suppressing mechanism. Various anticancer therapies induce senescence in malignant cells by inducing genotoxic stress, overactivating mitotic signals or inducing oxidative stress; this blocks the growth of tumor cells and promotes immune cell infiltration (74). However, some patients experience relapse, metastasis and/or therapeutic resistance. The TME is a complex biological system consisting of tumor cells and numerous nontumor components. These nontumor components, such as the ECM, fibroblasts and immune cells, can have profound effects on tumor progression during aging (75,76). This review focuses on the impact of aging of CAFs on tumor progression.

CAFs and senescence. Tumor cells can induce the aging of stromal cells through cytokine secretion. It has been reported that the specific expression of matrix metalloproteinase 1 in large-cell carcinoma can induce fibroblast senescence and promote the progression of lung cancer (76). In addition, the gut microbiota can induce aging of hepatic stellate cells through the enterohepatic circulation of metabolites, leading to the development of liver cancer (77-79). Cancer cells cease to proliferate after TIS; however, senescent cells still exhibit metabolic activity and undergo changes in their secretory proteomes. They secrete proinflammatory factors, growth factors and proteases, collectively referred to as SASP (80). The accumulation of therapy-induced senescent cells leads to chronic inflammation and immunosuppression, which can have long-term adverse effects (74). Since most anticancer treatments are administered systemically, they become problematic when nonmalignant cells in nontumor areas undergo senescence in response to these therapies (81). The present review aims to concentrate on recent studies that refer to the induction of senescence in CAFs by antitumor therapies, such as chemotherapy, radiotherapy (RT) and targeted therapies.

Cancer therapies and the induction of senescence

CAFs and chemotherapy. Chemotherapy and RT are conventional and widely utilized treatments for cancer. High doses of chemotherapy or RT can effectively induce the apoptosis of cancer cells; however, they also pose a risk of damaging the surrounding tissues, causing serious side effects in patients (74). Consequently, an alternative therapeutic strategy is to induce senescence in malignant cells to permanently halt their ability to proliferate without triggering apoptosis. An extensively studied mechanism of cellular aging is activation of the DNA damage response (DDR) (7). The DDR is closely associated with the relapse and development of tumors, and it also provides therapeutic opportunities for tumor treatment (82). When cells are exposed to various endogenous and exogenous stressors (such as replication stress, ultraviolet, drugs and ionization radiation), DDR-associated proteases (such as ATM, ATR, CHK1 and PARP) are activated, which eventually results in senescence (83). Camptothecin, doxorubicin and etoposide, the most commonly used topoisomerase inhibitors in chemotherapy for various types of cancer, can effectively block DNA replication by causing misalignment of DNA strands after supercoil unwinding (84). Similarly, bioalkylating agents, another widely used type of chemotherapeutic drug, trigger DNA damage-mediated aging reactions by causing DNA strand crosslinking, abnormal base pairing or DNA strand breaks. During cell division, these crosslinked

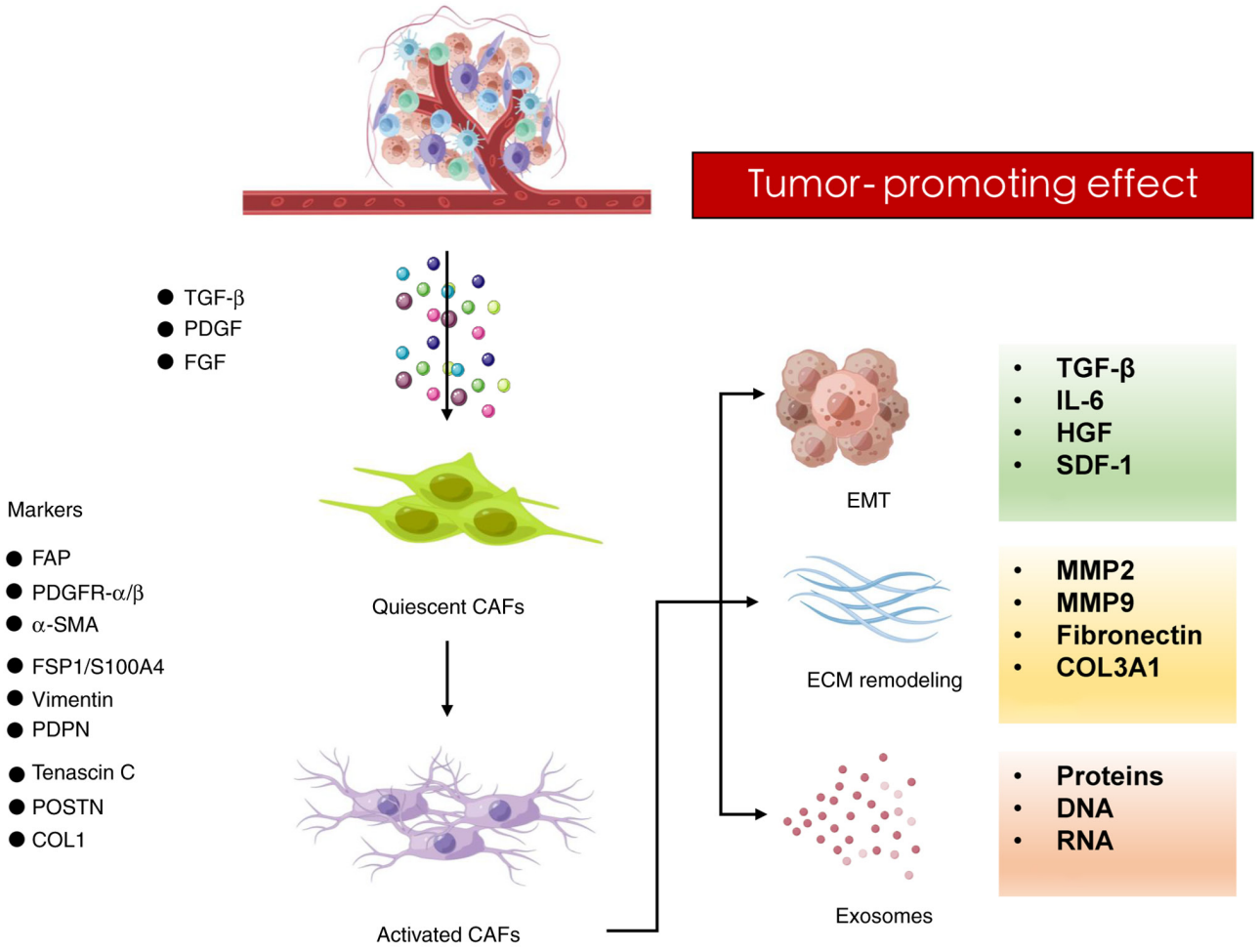

Figure 2. Tumor-promoting role of CAFs in the TME. TME-derived cytokines, such as TGF-β, PDGF and FGF, can transform quiescent CAFs into activated CAFs. Activated CAFs promote EMT of cancer cells by releasing prometastatic mediators, such as TGF-β, IL-6, HGF and SDF-1. In addition, activated CAFs can also remodel the ECM by secreting extracellular matrix-degrading enzymes, such as MMPs, to create tracks for cancer cell invasion. Furthermore, exosomes released by CAFs contain various proteins, DNA and non-coding RNA that are important in tumor progression. α-SMA, α-smooth muscle actin; CAFs, cancer-associated fibroblasts; COL, collagen; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FAP, fibroblast activation protein; FGF, fibroblast growth factor; FSP1, fibroblast-specific protein 1; HGF, hepatocyte growth factor; IL-6, interleukin-6; MMP, matrix metalloprotease; PDGF, platelet-derived growth factor; PDGFR, PDGF receptor; PDPN, podoplanin; POSTN, periostin; SDF-1, stromal cell-derived factor-1; TME, tumor microenvironment; TGF-β, transforming growth factor β.

DNA strands break, triggering DDR-mediated senescence. Cisplatin is an alkylating agent widely used in anticancer treatments (85). Microtubule inhibitors, such as paclitaxel can arrest tumor cells in the mitotic phase by disrupting the regular dynamics of microtubule spindles (86). These cytotoxic compounds, commonly used as standard cancer therapies for various tumor types, have dual effects. They induce a senescent phenotype in cancer cells and exert an anticancer effect. However, they also induce senescence in cellular components of the TME. CAFs play an essential role in promoting tumorigenic signals inside the tumor stroma. Senescent CAFs can enhance the differentiation and proliferation of neighboring tumor cells via the secretion of SASP factors. In a xenotransplant tumor model of breast cancer, senescent fibroblasts have been reported to promote the growth of breast cancer in mice through the secretion of matrix metalloproteinases (86). It has also been demonstrated that CAFs are prone to p53-mediated senescence during chemotherapy, leading to drug resistance in mouse lung cancer models (87). Similarly, a recent study revealed that docetaxel and cisplatin treatment can strongly induce a senescence phenotype in prostate- and ovary-associated fibroblasts *in vitro*. These senescent fibroblasts exhibit enhanced malignant behavior through alterations in metabolism and activation of SASP (88).

CAFs and RT. RT is a commonly used treatment for various types of cancers as it causes irreparable damage to cancer cell DNA. Similar to chemotherapy, the outcome of RT, whether senescence or apoptosis is induced, is mostly dependent on the radiation dose. High doses of radiation (>10 Gy) trigger apoptosis, whereas medium doses (>0.5 Gy) primarily lead to senescence (87). Unlike chemotherapy, RT can be administered directly to the cancer site, resulting in less damage to normal tissues. However, the tissues surrounding the tumor may still be affected, leading to a greater burden on aging cells and other local side effects (89). It has been shown that in murine rectal cancer models, tumor organoids and primary stromal cells derived from patients, CAFs undergo oxidative DNA damage following RT. This damage leads to p53-mediated senescence of CAFs, ultimately resulting in

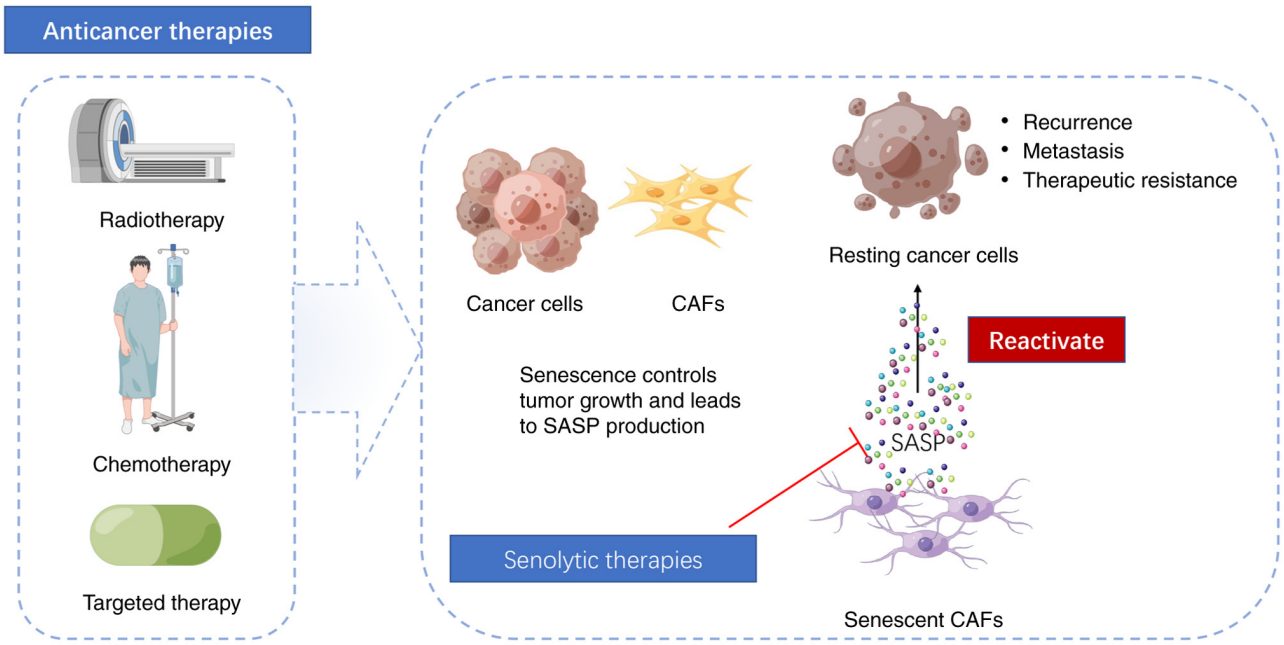

Figure 3. Future strategies to target aging cells in tumors. Systemic anticancer therapies cause the senescence of cancer cells to control tumor growth, and trigger the development of senescence of CAFs in the TME, resulting in SASP production, which can lead to tumor recurrence, metastasis and therapeutic resistance by reactivating dormant tumor cells. Senolytic drugs can selectively target aging cells and minimize side effects. CAFs, cancer-associated fibroblasts; SASP, senescence-associated secretory phenotype; TME, tumor microenvironment.

resistance to chemoradiotherapy and disease progression (67). Similarly, another study demonstrated that CAFs acquire senescence-like characteristics after RT, promoting lung cancer cell proliferation and radioresistance via activation of the JAK/STAT pathway (90).

CAFs and cell cycle inhibition. Cyclin-dependent kinase (CDK) inhibitor proteins are upregulated in senescent cells. CDK4/6 enzymes play a crucial role in facilitating the transition of the cell cycle from the G_1 phase to the S phase (91). In a number of cancer cells, particularly in breast cancer, the CDK4/6 axis is overactivated; therefore, targeting CDK4/6 is a promising anticancer strategy (92). CDK4/6 inhibitors (such as palbociclib, abemaciclib and ribociclib) have been approved for cancer treatment. By mimicking the function of p16 (INK4a), CDK4/6 inhibitors induce cell senescence and arrest the cell cycle (93). Data from *in vitro* models have demonstrated that palbociclib (PD-0332991) can cause senescence in normal fibroblasts. These aging fibroblasts significantly promote breast cancer development (94). Another study revealed that prolonged use of the CDK4/6 inhibitor palbociclib (PD-6) causes aging and induction of the SASP phenotype in normal fibroblasts, and that aging fibroblasts can promote melanoma progression in both *in vivo* and *in vitro* melanoma models. The study also revealed that this senescence is associated with the downregulation of Mdm2 rather than DNA damage (95).

5. One-two punch model for cancer treatment

The clinical dose of cancer therapy, while effectively inducing tumor cell apoptosis or senescence (first punch), can also lead to senescence of other elements in the TME, which can contribute to tumor relapse, metastasis and the development of drug resistance to cancer treatment. Eliminating these senescent cells is crucial for reducing the risk of tumor progression (second punch) (5). Senolytics, which are a type of drug that selectively eliminates aging cells, have emerged as potential therapeutics for addressing this issue. In the context of tumors, senolytic strategies typically involve a combination of a senescence-inducing drug and another drug targeting senescent cells to induce the synthesis of lethal substances. By specifically targeting and eliminating these senescent cells, senolytics hold promise in preventing tumor progression and improving the efficacy of cancer treatment. A key characteristic of aging cells is the alteration of chromatin structure, which affects gene expression. The present review aims to provide a brief introduction to the application of senolytic drugs in targeting senescent fibroblasts or stromal cells in tumors. However, there are detailed studies that focus on the introductions and applications of these drugs in other diseases (96,97).

Studies have revealed that the expression of anti-apoptotic proteins often increases in senescent cells (74,98). Senolytic drugs can target upregulated anti-apoptotic pathways in senescent cells and reactivate the apoptotic pathway to eliminate aging cells (99). Navitoclax, a selective BCL inhibitor, is primarily active against BCL family members (such as BCL-2, BCL-XL and BCL-W). When used in combination with anticancer treatments, navitoclax can potentially achieve a dual effect. In a cell line and mouse model of glioblastoma, extensive senescence has been shown to occur in the brain following RT. Aging stromal cells promote the aggressive phenotype of glioblastoma via SASP, which enhances its ability to invade and migrate *in vitro* and *in vivo*. However, the use of navitoclax (ABT-263) selectively eliminates the senescent cells and significantly reduces glioma cell growth (100).

Quercetin, a natural flavonol compound, and dasatinib, a tyrosine kinase inhibitor, are widely used to target senescent cells by interfering with Src and PI3K signaling. In a liver cancer mouse model, dasatinib has been reported to effectively inhibit senescent stellate cells, thereby inhibiting tumor progression (101). FOXO4-DRI, an interfering peptide that can regulate the activity of p53, disrupts the interactions between p53 and FOXO4. This selective disruption leads to p53 nuclear exclusion and apoptosis of senescent cells (102). Research has demonstrated that RT can induce senescence-like characteristics of CAFs in non-small cell lung cancer. FOXO4-DRI enhances the radiosensitivity of NSCLC cells and alleviates RT-induced pulmonary fibrosis by targeting aging CAFs, both *in vitro* and *in vivo* (90) (Fig. 3).

6. Conclusions and future perspectives

The goal of tumor therapy is to achieve a complete cure by eliminating malignant tumors. Increasing attention has been paid to the function of the TME in tumor therapies, as it can significantly impact therapeutic outcomes. Systemic anticancer therapy induces senescence in cancer cells and triggers the development of aging components in the TME. Among these components, CAFs are critical in tumor progression. The one-two punch strategy aims to address the dual behavior of TIS, which can have both favorable and unfavorable effects on tumor therapies. This approach acknowledges both the positive outcomes and the possible challenges associated with senescence induction. By targeting both the beneficial and harmful effects of TIS, this strategy can provide significant therapeutic benefits and may be an effective approach for future studies on cancer treatment.

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Availability of data and materials

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Authors' contributions

QZ and YL were involved in study conceptualization. HF and SS contributed to the generation of the figures and table. RJ performed the literature investigation. QZ and YL wrote the original draft. YJ reviewed and edited the manuscript. ZC supervised the study. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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