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REVIEW

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Regulation of cellular senescence in tumor progression and therapeutic targeting: mechanisms and pathways

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Abstract

Cellular senescence, a stable state of cell cycle arrest induced by various stressors or genomic damage, is recognized as a hallmark of cancer. It exerts a context-dependent dual role in cancer initiation and progression, functioning as a tumor suppressor and promoter. The complexity of senescence in cancer arises from its mechanistic diversity, potential reversibility, and heterogeneity. A key mediator of these effects is the senescence-associated secretory phenotype (SASP), a repertoire of bioactive molecules that influence tumor microenvironment (TME) remodeling, modulate cancer cell behavior, and contribute to therapeutic resistance. Given its intricate role in cancer biology, senescence presents both challenges and opportunities for therapeutic intervention. Strategies targeting senescence pathways, including senescence-inducing therapies and senolytic approaches, offer promising avenues for cancer treatment. This review provides a comprehensive analysis of the regulatory mechanisms governing cellular senescence in tumors. We also discuss emerging strategies to modulate senescence, highlighting novel therapeutic opportunities. A deeper understanding of these processes is essential for developing precision therapies and improving clinical outcomes.

Keywords Cellular senescence, Tumor, Therapy, DNA damage, SASP

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Introduction

Cellular senescence is a stable state of cell cycle arrest, characterized by distinct morphological changes, altered metabolism, gene expression patterns, and a secretory phenotype known as the senescence-associated secretory phenotype (SASP). Senescence can be triggered not only by intrinsic mechanisms such as the cellular division limit (replicative senescence), but also by extrinsic factors like culture conditions (premature senescence) [1]. The impact of cellular senescence on the human body extends across various physiological processes, including embryonic development, wound healing, tumor suppression, and immune regulation [2]. Furthermore, senescence is implicated in the development of numerous diseases, such as cancer, cardiovascular disease and neurodegenerative disorders [3–5].

In recent decades, cellular senescence has emerged as a focal point in cancer research. Initially, it was discovered that p53-mediated senescence serves as a critical natural barrier against tumorigenesis, as p53 activation inhibits abnormal cell proliferation [6]. As research progresses, more mechanisms of tumor cell senescence have been discovered, including telomere shortening, oxidative stress, and oncogene activation. These mechanisms are precisely regulated through complex and overlapping signaling pathways.

This article aims to review the molecular mechanisms of cellular senescence in tumor progression and provide an overview of senescence-based therapies for tumors. By gaining a comprehensive understanding of the dual role of cellular senescence in tumors, a more rational approach can be developed to enhance therapeutic interventions (such as promoting senescence, eliminating senescence, and combining both therapies).

Milestones in the history of cellular senescence research

In 1961, Hayflick and Moorhead discovered that human fibroblasts cultured in vitro do not divide indefinitely but instead enter an irreversible state of proliferative arrest, a phenomenon now known as the Hayflick limit [7] (Fig. 1). Since then, scientists have referred to this phenomenon as cellular aging or cellular senescence. It is worth noting that the terms "cellular aging" and "cellular senescence" are not interchangeable. "Aging" refers to the gradual decline in bodily functions as an organism ages and accumulates damage. In contrast, "cellular senescence" specifically refers to a state in which cells permanently stop dividing in response to stress or damage, a process that can occur at any point during an organism's life [8]. Therefore, "cellular senescence" is a more precise term. In

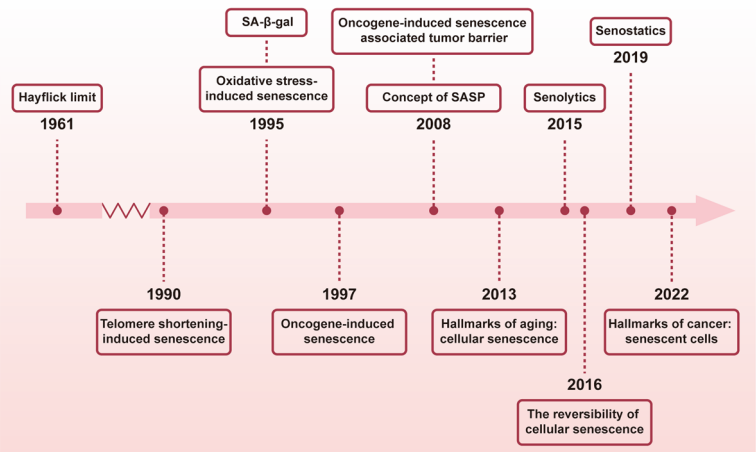

Fig. 1 Key milestones in the study of cellular senescence. This timeline highlights significant discoveries in cellular senescence research from 1961 to present. In 1961, the Hayflick Limit was established, demonstrating that human fibroblasts have a finite capacity for cell division, marking the discovery of replicative senescence. By 1990, telomere shortening was identified as a key mechanism underlying cellular senescence, providing an explanation for the Hayflick Limit. In 1995, senescence-associated β-galactosidase (SA-β-gal) was identified as a biomarker for cellular senescence, alongside findings that oxidative stress can induce cellular senescence. In 1997, activation of the RAS oncogene was shown to trigger cellular senescence. By 2008, the mechanisms underlying oncogene-induced senescence associated tumor barrier function were summarized. In the same year the focus of senescence research shifted from the phenomenon and mechanisms to exploring the functions and applications, spurred by the concept of the senescence-associated secretory phenotype (SASP). In 2013, cellular senescence was recognized as one of the Hallmarks of Aging. In 2015, the first senolytic agents, dasatinib and quercetin, were identified. In 2016, The potential reversibility of cellular senescence was found in cancer cells. In 2019, the concept of senostatics emerged, aimed at mitigating the adverse effects of senescent cells. Finally, in 2022, the role of senescent cells in cancer development was integrated into the latest Hallmarks of Cancer

1990, Calvin B. Harley demonstrated that the quantity and length of telomeric DNA in human fibroblasts decrease with cell division, promoting cellular senescence and elucidating the Hayflick limit [9]. In 1995, Gerardo Dimri and colleagues introduced senescence-associated β-galactosidase (SA-β-gal), a biomarker that identifies senescent cells [10]. In the same year, a study demonstrated that oxidative stress-induced DNA damage significantly contributes to cellular senescence [11]. In 1997, Manuel Serrano's research indicated that activation of the oncogene RAS can induce senescence in rodent cells [12]. Until 2008, oncogene-induced senescence associated tumor barrier functions were systematically reviewed and published in Science [13, 14]. In the same year, the concept of SASP was expanded, leading to a broader understanding of cellular senescence. It was no longer viewed as a passive state but one where senescent cells actively secrete factors that influence their surrounding tissue environment [15].As the role of cellular senescence in age-related diseases was gradually uncovered, it was included as one of the Hallmarks of Aging in 2013 [16]. In 2015, the team of Mayo Clinic and Scripps Research first found that the combination of dasatinib and quercetin selectively clear senescent cells [17]. A 2016 study reported that a subset of atypical cancerous cells, which strongly expressed p21, exhibited proliferative features after senescence, suggesting that cellular senescence is reversible [18]. In 2018, by studying the genetic lineage tracing of the fate of senescent cells in vivo, it was found that some senescent cells are not eliminated during mouse embryonic development and may re-enter the cell cycle after birth, thereby confirming the reversibility of senescence during embryonic development [19]. In 2019, summarized the drugs that can inhibit SASP such as rapamycin named senostatics, helping to block the adverse effects of senescent cells [20]. In 2022, the importance of senescent cells in cancer development was further recognized and incorporated into the latest Hallmarks of Cancer [21].

Inducing factors of cellular senescence

The occurrence of cellular senescence is driven by multiple factors, which can be categorized into environmental and host factors based on their origin.

Environmental factors

A variety of environmental factors, including biological, physical, chemical, and social factors, have been implicated in the acceleration of cellular senescence, possibly through direct cellular damage or altered cellular metabolism (Fig. 2).

Biological factors

Research studies have demonstrated that many pathogens, including bacteria, viruses, and fungi, can induce cellular senescence [22]. In vitro, the accumulation of bacterial lipopolysaccharide (LPS) in the cytoplasm activates the pattern recognition receptor (PRR) caspase-4, which subsequently triggers the p53-p21 and $p16^{INK4a}$-CDK4/6 pathways, leading to cellular senescence [23]. Studies on coronavirus disease 2019 (COVID-19) demonstrate that SARS-CoV-2 degrades the DNA damage-responsive kinase CHK1 in host cells, reducing DNA repair and upregulating $p16^{INK4a}$ expression. This process induces cellular senescence, which in turn triggers the secretion of pro-inflammatory cytokines, extracellular matrix remodeling factors, and pro-coagulatory mediators by senescent cells. These events contribute to a cytokine storm, which accelerates senescence in neighboring cells and leads to surrounding tissue damage [24–26]. Moreover, studies have shown that HIV can inhibit the PI3K/ATM pathway, leading to DNA damage and telomere attrition, which accelerates the senescence of CD4 + T cells, thus exacerbating immune system dysfunction in HIV infection [27]. In candidiasis, the upregulation of circular RNA circHIPK3 competitively binds miR-148b-3p, leading to increased expression of DNMT1/3a. This enhances methylation of the anti-aging gene Klotho promoter, reducing Klotho expression and ultimately promoting cellular senescence, which exacerbates the inflammatory response to infection [28].

Physical factors

Physical factors include mechanical stress, radiation, temperature, atmospheric pressure, electric currents, and noise (Fig. 2). For example, shear stress from surgical incisions can suppress the transcription of sirtuin 1 (SIRT1) in liver sinusoidal endothelial cells (LSECs), promoting the activity of proteins like p53, p21, and $p16^{INK4a}$, thereby accelerating LSEC senescence and impairing liver regeneration following partial hepatectomy [29]. Ultraviolet radiation (UVA and UVB), combined with urban particulate matter (UPM), can lead to mitochondrial dysfunction, elevation of reactive oxygen species (ROS), DNA damage, and can contribute to skin aging [30]. Heat exposure accelerates cellular metabolism, increasing ROS production and disrupting DNA replication. This activates the cyclic GMP-AMP synthase (cGAS) and stimulator of interferon genes (STING) pathways, promoting lung tissue aging and fibrosis [31].

Chemical factors

Chemical factors encompass both inorganic and organic compounds. Inorganic factors such as atmospheric

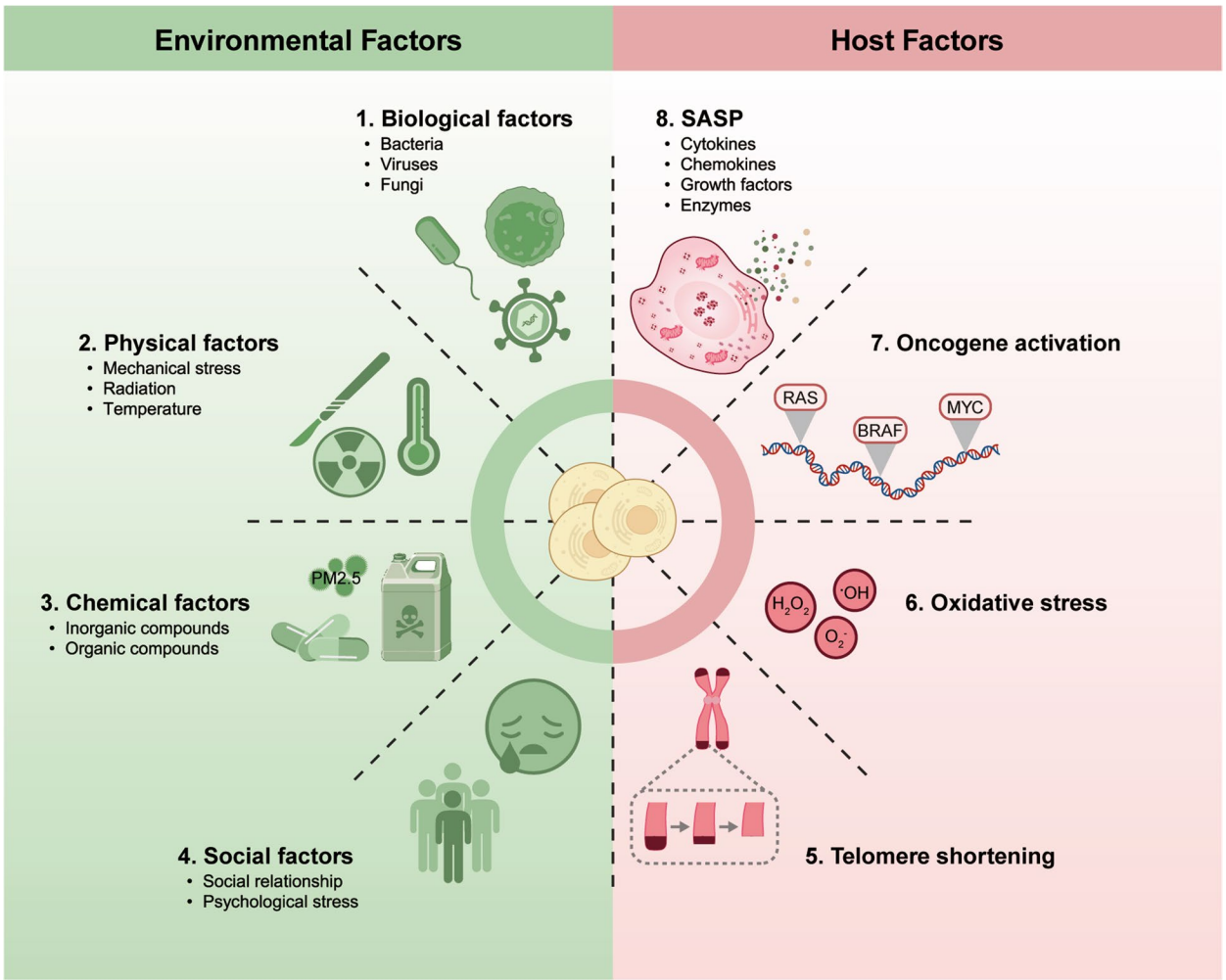

Fig. 2 Inducing factors of cellular senescence. Cellular senescence is driven by multiple factors, categorized as environmental and host factors based on their origin. Environmental factors include biological, physical, chemical, and social factors. Biological factors (1) include bacteria, viruses, and fungi. Physical factors (2) encompass mechanical stress, radiation, temperature, etc. Chemical factors (3) involve exposure to inorganic and organic compounds. Social factors (4) are reflected in the poor social relationship and the psychological stress. Host factors include telomere shortening (5), oxidative stress (6), oncogene activation (7) and SASP (8). Together, these factors orchestrate the complex mechanisms leading to cellular senescence

particulate matter (PM) have long been recognized as a threat to human health. Research has shown that PM exposure can induce replicative senescence (RS), which is associated with the downregulation of telomerase reverse transcriptase (TERT) and proliferating cell nuclear antigen (PCNA) in human lung epithelial cells [32]. PM exposure also inhibits the SIRT1/PGC-1α/SIRT3 signaling pathway, impairing the antioxidant system, which leads to ROS accumulation and promotes cellular senescence [33]. Zinc oxide (ZnO) nanoparticles (NPs), frequently used in cosmetics, agriculture, biosensors, and drug delivery, have been shown to induce mesenchymal stem cell senescence through oxidative stress and DNA damage [34].

Cannabidiol (CBD), an organic compound used in the treatment of childhood epilepsy, inhibits the expression of key proteins involved in DNA replication, including E2F1, E2F2, cyclin D3, and CDK2, resulting in cell cycle arrest. Additionally, CBD suppresses key enzymes in DNA repair pathways, ultimately activating a p53-dependent senescence pathway [35]. Additionally, certain chemotherapy drugs have been shown to induce senescence (therapy-induced senescence, TIS) in tumor cells. For example, doxorubicin, used in treating chronic myeloid leukemia (CML) in the K562 cell model, upregulates miR-375 and induces autophagy, leading to senescence, independent of the $p16^{INK4a}$ and p53 senescence pathways [36]. Prolonged exposure to bleomycin induces

oxidative stress and DNA double-strand breaks in alveolar epithelial cells, inhibiting Rad51 expression, impairing DNA repair, and triggering senescence, which leads to lung toxicity [37].

Social factors

Social factors refer to the functional or prescriptive effects of a person's social relationships, such as emotional support, instrumental help, and information. Systematic reviews indicate that poor social relationships, including negative perceptions of one's neighborhood, contribute to telomere shortening and accelerate physical aging [38]. Additionally, psychological stress has been identified as another factor that induces telomere shortening [39, 40]. For instance, loneliness and emotional distress can increase biological aging by 1.65 years, exceeding the influence of factors such as biological sex, living area, marital status, or smoking [41]. These findings underscore the importance of the biopsychosocial model in the etiology of cellular senescence.

Host factors

In addition to external environmental factors, cellular senescence is regulated by intrinsic stressors and damaging elements, collectively referred to as host factors in this paper. Specifically, host factors include telomere shortening, oxidative stress, oncogene activation, and SASP (Fig. 2).

Telomere shortening

The discovery of telomeres dates back to 1978, when Elizabeth Blackburn first identified a repetitive sequence of nucleotides at the ends of chromosomes in the protozoan Tetrahymena, marking the beginning of telomere research [42]. Telomeres are specialized DNA–protein complexes composed of hexameric TTAGGG nucleotide repeats and associated proteins in mammals, protecting chromosomal integrity [7, 43]. Telomere length is regulated by the activity of telomerase and shelterin complexes.

Telomerase is an enzyme complex consisting of TERT, telomerase RNA component (TERC), and associated cofactors. Telomerase synthesizes new DNA sequences to elongate telomeres, which counteracts the natural shortening of telomeres that occurs during cell division. The tumor suppressor liver kinase B1 (LKB1) enhances the transcription of Sp1, which inhibits TERT expression, leading to telomere shortening, promoting senescence in tumor cells, and inhibiting tumor growth [44].

The shelterin complex consists of six subunits: TRF1, TRF2, TIN2, Rap1, TPP1, and POT1 [45]. It binds to telomeric DNA associated with nucleosomes and inhibits the recognition of cellular DNA repair machinery. Studies have shown that external stimuli, such as radiation, oxidative stress, or bleomycin, can induce ubiquitination of telomere protection protein 1 (TPP1) by the E3 ubiquitin ligase FBW7, leading to TPP1 degradation and triggering telomere uncapping and the DNA damage response (DDR) [46]. Additionally, shelterin senses telomere length, regulates telomerase activity, and recruits telomerase to the telomere, coordinating the conversion of newly synthesized telomeric single-stranded DNA into double-stranded DNA [47].

Oxidative stress

ROS are reactive oxygen-containing molecules, including superoxide (O_2^-), hydrogen peroxide (H_2O_2), singlet oxygen ($1O_2$), and hydroxyl radicals (·OH) [48]. Major sources of ROS include mitochondria, NADPH oxidases (NOXs), the endoplasmic reticulum (ER), and peroxisomes. To maintain redox homeostasis, the intracellular antioxidant system, comprising various antioxidant enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase, and peroxiredoxin) and nonenzymatic molecules (e.g., glutathione, flavonoids, and vitamin C), dynamically regulates ROS levels and repair oxidative damage [49].

Oxidative stress is a condition characterized by an imbalance between ROS production and the antioxidant defense system's ability to detoxify these harmful molecules or repair the resulting damage. This state can lead to oxidative damage to biomolecules, including proteins, lipids, and DNA, and has been linked to cellular senescence [50]. For example, mitochondrial calcium overload can disrupt the electron transport chain (ETC) in cardiomyocytes, leading to excessive ROS production and damaging the DNA structure, ultimately triggering premature cardiac aging [51]. Furthermore, vanadate is found to directly oxidize and increase the efflux of glutathione (GSH) species, causing cellular senescence in lung fibroblast cells independent of ROS intermediates [52].

Oncogene activation

Oncogenic activation is a critical mechanism in tumor initiation and progression, driving cell growth and division. However, studies have shown that activated RAS can induce senescence in fibroblasts. Subsequent studies have confirmed and expanded this finding, demonstrating that other activated oncogenes, such as BRAF and MYC, can also induce replication stress, resulting in stable growth arrest in cultured cells [53–55] (Fig. 2).

RAS is a family of small GTPases, including HRAS, KRAS, and NRAS, that play a crucial role in regulating various cellular processes, such as growth, differentiation, and survival [56]. Upon activation, RAS interacts with several downstream effectors, most notably the

MAPK/ERK and PI3K-AKT pathways, leading to a cascade of signaling events that promote cell proliferation and survival [57, 58]. In various tumors, mutations or overexpression of RAS are commonly associated with constitutive activation, resulting in uncontrolled cell growth and proliferation. Aberrant proliferative signaling induces DNA replication stress and activates DDR, thereby leading to cellular senescence [59]. Furthermore, RAS-related pathways can also promote the metabolic production of ROS in cells, leading to the accumulation of ROS and exacerbating DNA damage [60, 61]. Other components of the RAS pathway, including RAF, RAC1, and MEK, may also induce cellular senescence [62, 63]. For instance, baicalin has been demonstrated to upregulate the expression of decidual protein induced by progesterone, which interacts with KRAS, activating the MAPK/ERK pathway and the $p16^{INK4a}$-CDK4/6 pathway, resulting in colon cancer cell senescence with an anti-cancer effect [64]. Similarly, BRAF, a member of the RAF kinase family, is commonly mutated at position V600E, triggering p53 and $p16^{INK4a}$-dependent senescence [65].

SASP

SASP refers to the secretion of a variety of pro-inflammatory and pro-senescence molecules, including cytokines, chemokines, matrix metalloproteinases (MMPs), and growth factors, by senescent cells. These secreted factors not only mark the senescent state but can also induce senescence in neighboring cells [66]. Pro-inflammatory cytokines like IL-6 and IL-8 sustain and amplify inflammatory responses through autocrine and paracrine signaling, exacerbating tissue damage. This chronic inflammation, known as "inflammaging," can further activate DDR, driving cells into senescence [67]. The long-term presence of inflammatory mediators also leads to the inhibition of antigen presentation and immune cell differentiation, thereby impairing the ability of the immune system to clear senescent or damaged cells, further perpetuating the cycle of inflammation and senescence [68]. Moreover, this chronic inflammatory environment can foster tumor growth by supporting cell proliferation, angiogenesis, and metastasis [69, 70]. Additionally, matrix-degrading enzymes disrupt the extracellular matrix, impair tissue architecture, and induce DNA damage in surrounding cells, ultimately promoting senescence in neighboring cells [71, 72].

In summary, cellular senescence arises from a complex interplay of various factors. Environmental factors can induce telomere shortening, disrupt redox balance, and activate oncogenes, thereby triggering the activation of senescence pathways. Simultaneously, host factors contribute to cellular senescence through gene regulation, metabolic buildup, and DNA damage. These factors interact synergistically, thereby shaping the pathways of senescence.

Mechanisms of senescence

The molecular mechanisms underlying cellular senescence are complex and diverse, which can be categorized into two main classes: DNA damage-induced senescence and non-DNA damage-induced senescence. DNA damage-induced senescence is primarily driven by factors such as telomere shortening, oxidative stress, and oncogene activation, while non-DNA damage mechanisms promote senescence by regulating key molecules including $p16^{INK4a}$ and SASP.

DNA damage-induced cellular senescence

Cellular DNA is frequently subjected to damaging events from both environmental factors and intrinsic factors as mentioned previously. DNA damage can be broadly classified into two categories: (1) lesions affecting a single strand of the double helix, such as modified bases, abasic sites, helix-distorting base lesions, and single-strand breaks (SSBs); (2) lesions involving both strands, including interstrand crosslinks and double-strand breaks (DSBs) [73]. In response, cells activate DNA repair pathways to remove lesions. When damage cannot be effectively repaired, it can lead to genomic instability and trigger signaling cascades, ultimately resulting in cellular senescence or apoptosis [74]. This phenomenon, where DNA damage induces senescence, is termed DNA damage-induced cellular senescence (Fig. 3). This type of senescence can be categorized based on its origin into RS, telomere dysfunction-induced senescence, oxidative stress-induced senescence (OSIS), oncogene-induced senescence (OIS), and TIS. RS refers to the gradual shortening of telomeres in normal cells as the number of divisions increases, leading to DNA damage and cell cycle arrest [75, 76]. Telomere dysfunction-induced senescence, on the other hand, refers to the process in which telomere shortening and cellular senescence are triggered by dysfunction of telomerase and the shelterin, often due to factors other than normal division [77–79]. OSIS results from oxidative damage that compromises DNA integrity and repair mechanisms [80]. OIS is triggered by oncogene activation, causing replication stress, oxidative stress and DDR [12, 81]. TIS arises from cancer therapies, including chemotherapy and radiation, which induce DNA damage and promote senescence in tumor cells [82].

Severe types of DNA damage, particularly SSBs and DSBs, are more likely to trigger cellular senescence.

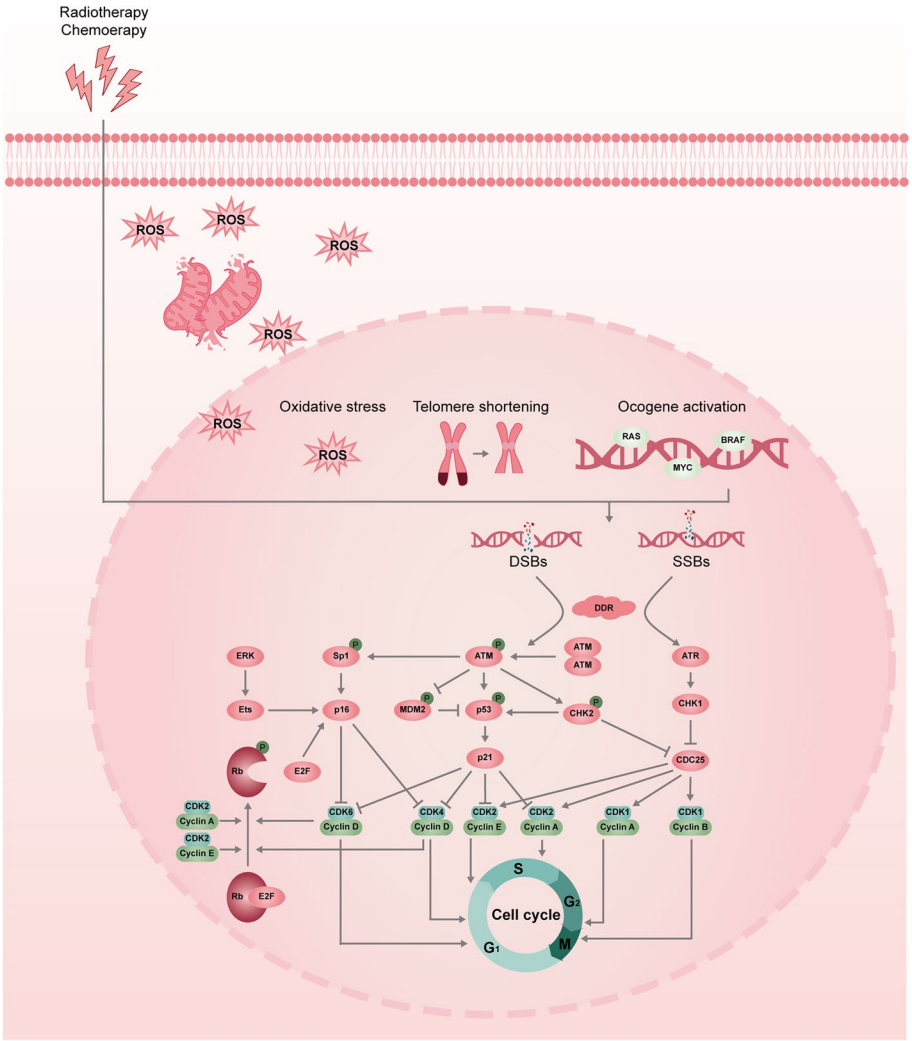

Fig. 3 Pathways of DNA damage-induced cellular senescence. DNA damage is a critical event that can arise from various sources, including cancer therapies, oxidative stress, telomere shortening, and oncogene activation. In response to DNA damage, cells activate a series of signaling pathways collectively known as the DNA damage response (DDR). Severe types of DNA damage, particularly SSBs and DSBs, are more likely to trigger cellular senescence. SSBs activate the ATR-CHK1 pathway, which inhibits CDC25 and subsequently suppresses the CDK1/Cyclin A and CDK1/Cyclin B complexes, thereby blocking G2/M transitions and inducing cell cycle arrest. In the case of DSBs, the ATM-CHK2 axis activates p53, leading to p21 induction, which suppresses CDK4/6-Cyclin D and CDK2-Cyclin E/A complexes, driving senescence. Phosphorylated CHK2 also inhibits CDC25, blocking the activation of CDK1 and CDK2, inducing cell cycle arrest. Additionally, ATM also stabilizes p53 by inhibiting MDM2, further enhancing p53-mediated senescence. Moreover, Sp1 activated by ATM, Ets activated by ERK as well as the accumulation of E2F activate $p16^{INK4a}$, which binds to CDK4/6, preventing their association with Cyclin D and further inhibiting Rb phosphorylation, then reinforcing cell cycle arrest

Following the formation of SSBs, ataxia-telangiectasia and Rad3-related protein (ATR) is recruited to the damage site or replication stress by its partner protein ATRIP, which facilitates ATR's binding to replication protein A (RPA)-coated single-stranded DNA. ATR is subsequently activated by topoisomerase-binding protein 1 (TOPBP1), which phosphorylates and activates CHK1 [83]. Phosphorylated CHK1 inhibits the phosphatase CDC25, a group of phosphatases including CDC25A, CDC25B, and CDC25C, thereby preventing the activation of the CDK1-cyclin A/B complexes, obstructing the transition from G2 to M phase, ultimately leading to senescence [84, 85].

After DSBs occur, the Mre11-Rad50-Nbs1 (MRN) complex first reaches the damage site and uses its nuclease activity to recognize the broken ends. Subsequently, the MRN complex interacts with ataxia-telangiectasia mutated kinase (ATM), promoting its dimer dissociation into monomers and triggering ATM autophosphorylation, thereby activating ATM [86]. ATM is a key protein

kinase that detects DSBs and initiates the DDR by phosphorylating essential proteins, including CHK2 and p53. Upon DSB formation, the MRN complex (MRE11-RAD50-NBS1) recruits ATM to the damage site and facilitates ATM autophosphorylation, leading to the dissociation of its dimer into active monomers[87]. Activated ATM phosphorylates downstream targets such as CHK2 and p53 [88] (Fig. 3). Phosphorylated CHK2 inhibits CDC25A and CDC25C, blocking the activation of CDK2 and CDK1, which results in cell cycle arrest [89, 90]. Furthermore, activated CHK2 phosphorylates p53 at Ser20, enhancing its stability and transcriptional activity [91]. ATM also directly phosphorylates p53 at Ser15 and inhibits MDM2, preventing it from ubiquitinating p53, which further promotes p53 accumulation [92]. Additionally, ATM enhances p53's transcriptional activity by inhibiting the SIRT1 deacetylase activity, which is regulated by LARP7 [93]. p53 stimulates the expression of the cyclin-dependent kinase inhibitor p21, which binds to CDK2, inhibiting the CDK2-cyclin E/A complex while also blocking the CDK4/6-cyclin D complex. This dual inhibition prevents the cell cycle from progressing from the G1 to S phase, ultimately resulting in cellular senescence [94]. The retinoblastoma protein (RB) is a crucial downstream target of cyclin-dependent kinases (CDKs) in cell cycle regulation. As the cell cycle progresses, RB is phosphorylated by the CDK2-cyclin E/A complex and the CDK4/6-cyclin D complex, facilitating the release of E2F and the transition to the S phase. When CDK complexes are inhibited, hypophosphorylated RB binds to E2F transcription factors, blocking E2F-mediated transcription of genes essential for cell cycle progression [95]. Additionally, ATM directly phosphorylates the transcription factor Specificity Protein 1 (Sp1) at Ser101, enhancing its transcriptional activity. Phosphorylated Sp1 subsequently upregulates DDR genes, including $p16^{INK4a}$, promoting cellular senescence [96, 97].

Non-DNA damage-induced cellular senescence

In addition to DNA damage, non-DNA damage signals significantly contribute to cellular senescence. A key pathway involved in non-DNA damage-induced senescence is the $p16^{INK4a}$-CDK4/6 pathway. When cells detect excessive proliferative signals, $p16^{INK4a}$ activity is upregulated, forming a negative feedback mechanism to suppress uncontrolled proliferation. This mechanism is particularly important in response to oncogenic activation. During periods of excessive cell proliferation, hyperphosphorylated Rb releases more E2F transcription factors, which activate $p16^{INK4a}$ transcription. $p16^{INK4a}$ then binds to CDK4 or CDK6, preventing their association with cyclin D. This inhibits the phosphorylation of Rb by the CDK4/6-cyclin D complex, ultimately suppressing the cell cycle [98, 99]. Additionally, transcription factors from the Ets family, such as Ets1 and Ets2, are activated by the MAPK/ERK pathway, and bind to the $p16^{INK4a}$ promoter, further increasing its expression [100].

SASP factors operate upstream in multiple signaling pathways and have broad-reaching effects. Released by primary senescent cells, these factors induce senescence in neighboring cells through a process known as Paracrine Senescence (PS) [101]. The signaling pathways activated by SASP factors are diverse and largely independent of DNA damage. For instance, the secreted cytokine TGF-β binds to receptors on adjacent cells, activating receptor-regulated SMADs (such as SMAD2 and SMAD3), which form complexes with SMAD4 and translocate into the nucleus, enhancing the expression of p21 and p15, thus inducing senescence [102]. TGF-β also activates the PI3K/AKT pathway, upregulating the expression of ubiquitin-specific protease 15 (USP15), which stabilizes p53 through deubiquitination [103]. Similarly, the SASP factor IL-6 can bind to the gp130 subunit of its receptor, activating JAK-STAT3 pathways. This activation upregulates p21 expression and promotes senescence [104].

Characteristics and detection indexes of senescent cells

Cellular senescence is characterized by distinct morphological, molecular, and metabolic changes. Understanding these features facilitates the effective identification of senescent cells. The following are common characteristics of cellular senescence along with their respective detection indicators (Fig. 4).

Cellular morphological changes

Morphological alterations represent a key characteristic of senescent cells, especially in tumor cells, and are associated with a diminished capacity for proliferation. Senescent cells typically display enlargement, flattening, and increased dispersion [105]. These changes correlate with the accumulation of cofilin-1 and the hyperphosphorylation of microtubule-associated protein tau in senescent cells. These modifications enhance the rigid cytoskeletal structures formed by actin filaments, microtubules, and intermediate filaments [106]. Moreover, the accumulation of cytoplasmic particles, such as lipofuscin, in senescent cells represents a significant morphological change that can be clearly observed in histological sections. Lipofuscin is a pigment composed of oxidatively damaged lipids, proteins, and other metabolites. Its accumulation typically occurs in senescent cells due to a weakened clearance mechanism, particularly the reduced function of lysosomes. Currently, Sudan Black B (SBB)

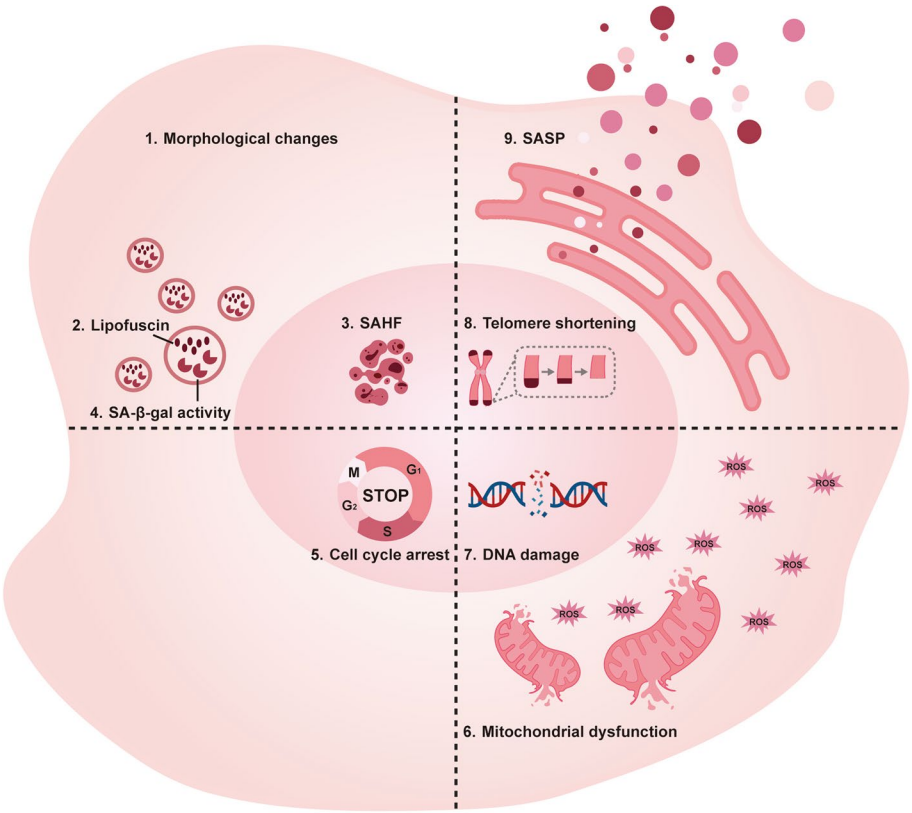

Fig. 4 Characteristics of senescent cells. Senescent cells exhibit distinct morphological, metabolic and functional changes. Main morphological changes (1) include cell enlargement, flattening, lipofuscin (2) and the formation of senescence-associated heterochromatin foci (SAHF) (3). Another defining characteristic of senescent cells is their stable cell cycle arrest (4). The lysosomal enzyme SA-β-gal becomes increasingly active during senescence and serves as a reliable marker for this state (5). Additionally, senescent cells exhibit mitochondrial dysfunction (6), resulting in the accumulation of ROS and oxidative stress. DNA damage (7), indicated by γ-H2AX foci, serves as an additional hallmark of senescent cells. When telomeres reach a critically short length (8), they trigger a DNA damage response that leads to cell cycle arrest. Furthermore, senescent cells secrete pro-inflammatory cytokines, chemokines, and proteases, collectively termed the senescence-associated secretory phenotype (SASP) (9)

and its analogues are the most widely used methods for detecting lipofuscin. SBB specifically binds to oxidized lipids and lipoproteins in lipofuscin, forming a dark precipitate that can be directly observed under an optical microscope [107–111]. Beyond these cellular changes, nuclear morphology serves as a predictive biomarker of senescence, particularly through chromatin remodeling. These changes are primarily characterized by the formation of heterochromatin regions, alterations in histone modifications, and the suppression of gene transcription [112, 113]. SAHF are unique chromatin structures found in senescent cells and can be detected using immunofluorescence staining techniques [114]. SAHF plays a crucial role in silencing genes related to cell proliferation, such as E2F target genes, thereby preventing further cell division [62]. Researchers observe that cellular senescence in breast cancer leads to the formation of distinct SAHF foci and an upregulation of H3K9me3. Chromatin remodeling inhibits the expression of cell cycle-related genes, prompting cancer cells to enter an irreversible state of arrest [115].

Cell cycle arrest

A hallmark of senescent cells is their inability to continue dividing, often halting at the G1 or G2/M phase of the cell cycle. This arrest is mediated by altered cell cycle regulatory mechanisms that prevent senescent cells from entering the S phase for DNA replication (Fig. 4). As previously discussed, several cell cycle inhibitors, including p53, p21, and $p16^{INK4a}$, impede cell division by inhibiting cyclin-CDK complexes. For instance, studies show that inhibition of the enhancer of zeste homolog 2 (EZH2) in gastric cancer cells leads to increased expression of p21 and $p16^{INK4a}$, resulting in irreversible G1 phase arrest and initiation of cellular senescence [116]. Techniques like western blotting and quantitative polymerase chain reaction (qPCR) are commonly used to measure the expression levels of these inhibitors, providing insights into

tumor proliferative activity and the onset of senescence [117, 118].

Cellular metabolic changes

With the occurrence of senescence, the metabolism of cells undergoes significant changes, which not only impair the cell's own function but also affect the overall health of the surrounding microenvironment and tissues. Common metabolic characteristics of senescent cells include enhanced glycolysis [119], lipid accumulation [120], alterations in amino acid metabolism [121], and an imbalance between oxidative stress and antioxidant defense due to mitochondrial dysfunction [122]. In addition, senescent cells also have unique protein alterations, among which the change in β-galactosidase activity is an important indicator for detecting senescent cells.

β-galactosidase is a hydrolase enzyme commonly used as a classic biomarker for cellular senescence [123]. The number and size of lysosomes increase in senescent cells, and SA-β-gal, as a lysosomal enzyme, becomes more active during the senescence process. In tumor cells, SA-β-gal activity is frequently used to evaluate whether treatment strategies induce senescence in cancer cells [124]. The most widely used method for detecting SA-β-gal is X-gal staining, a chemical reaction that produces a blue product through hydrolysis. At pH 6.0, SA-β-gal in the cells hydrolyzes X-gal, resulting in blue spots observable under a light microscope. For more sensitive and quantitative detection of SA-β-gal, especially in high-throughput screening, fluorescence-based assays have also been employed [125].

SASP

Once cells enter a senescent state, they secrete various pro-inflammatory cytokines, chemokines, proteases, and other molecules collectively known as the SASP [126]. In senescence induced by genotoxic stress, the p38 mitogen-activated protein kinase (p38MAPK) pathway is activated, regulating the mRNA levels of SASP factors such as GM-CSF, IL-6, IL-8, GROα, MCP-2, and IL-1α [127]. Additionally, the cGAS-STING pathways also play critical roles in this process [128]. The SASP enables senescent cells to transmit damage signals to surrounding cells or tissues, promoting a series of immune responses [129, 130]. However, when senescent cells are not promptly cleared, sustained secretion of the SASP creates a growth-stimulatory and immunosuppressive microenvironment that supports tumor development [5, 131]. For instance, SASP factors like IL-6 and IL-8 are prominently expressed in senescent tumor cells, promoting inflammation and angiogenesis in the microenvironment [132]. Given that the expression of SASP factors is often elevated in senescent cells, monitoring these factors through techniques such as ELISA, qPCR, or western blotting can provide valuable insights into cellular senescence. However, the SASP of senescent cells exhibits diverse and unstable characteristics, complicating their identification with a single, universal, or model-specific biomarker. Thus, a combination of multiple detection indicators is necessary for the accurate identification of senescent cells in tissues [133].

DNA damage

As mentioned earlier, in response to DNA damage, cells initiate a series of protective mechanisms, collectively known as the DDR. When DDR is activated but fails to repair the damage, the stress may drive cells to enter senescence. This process is accompanied by the activation of DNA damage markers such as 53BP1 and γ-H2AX, which can be detected by immunofluorescence to identify senescent cells [134, 135]. Additionally, because telomere shortening can also induce DNA damage and promote cellular senescence, telomere length is commonly used as an auxiliary marker for detecting senescent cells.

It is worth noting that, to date, no single biomarker has been proven sufficient to reliably detect cellular senescence in vivo, and a combination of multiple biomarkers remains necessary [109]. The biomarkers currently widely accepted for indicating the presence or absence of senescent cells are listed below (Table 1).

Reversibility of cellular senescence

Since 1961, cellular senescence has commonly been defined as a state in which a cell undergoes irreversible cell cycle arrest following prolonged division or exposure to various forms of stress, with cyclin dysregulation playing a critical role. However, the view of senescence as a strictly irreversible phenomenon has been increasingly questioned [170]. As noted above, the p53-p21 and $p16^{INK4a}$-CDK4/6 pathways are critical regulators of cellular senescence, acting to inhibit the activity of CDK-cyclin complexes and thereby arresting the cell cycle. Yet, in cases where p53 is ineffective or inactivated, particularly in certain tumors, the cellular response to DNA damage becomes less stringent [171, 172]. In such cases, p21 may promote genomic instability, leading to the accumulation of DNA damage and impairing the progression of the senescence program. As a result, tumor cells in a senescent state may bypass the senescence barrier, producing more aggressive progeny and facilitating tumor progression [173]. Experimental evidence shows in p53-deficient lung cancer cells, p21-mediated senescence can be reversed. This occurs through the upregulation of replication factors, such as Cdt1 and Cdc6,

Table 1 The main markers of senescent cells

Characteristic	Senescence marker	Detection method	Ref.
The metabolic changes	SA-β-gal	Histochemical staining, fluorescence staining, colorimetry, TEM	[136–139]
Cell cycle arrest	$p16^{INK4a}$	IHC, flow cytometry, WB, RT-qPCR, microarray, RNA sequencing	[140–143]
	p21	IHC, flow cytometry, WB, RT-qPCR, microarray, RNA sequencing	[140, 142–144]
	p53	IHC, flow cytometry, WB, RT-qPCR, microarray, RNA sequencing	[14, 145, 146]
	LaminB1	IHC, flow cytometry, WB, IF, qPCR	[147–149]
	Rb	IHC, flow cytometry, WB, IF, qPCR	[150–152]
DNA damage	γ-H2AX	IF, WB, flow cytometry, Co-IP, ChIP	[136, 140, 153]
	53BP1	IF, WB, flow cytometry, Co-IP, ChIP	[140, 154, 155]
	Telomere length	TRF assay, qPCR, TeSLA, telomere Profiling, STELA, FISH	[156–159]
Morphological and metabolic changes	SAHF	IF, confocal microscopy, ChIP	[62, 160, 161]
	Lipofuscin	Histochemical staining, fluorescence staining, SBB	[107–111]
SASP	IL-6	ELISA, CLIAs, WB, flow cytometry, IHC	[162–165]
	IL-8	ELISA, CLIAs, WB, flow cytometry, IHC	[166–168]
	IL-23R	ELISA, FISH	[169]

TEM Transmission electron microscopy, *IHC* Immunohistochemistry, *WB* Western blotting, *RT-qPCR* Reverse transcription quantitative real-time polymerase chain reaction, *IF* Immunofluorescence, *Co-IP* Co-immunoprecipitation, *ChIP* Chromatin Immunoprecipitation, *TRF* Telomere restriction fragment, *qPCR* Quantitative polymerase chain reaction, *TeSLA* Telomere shortest length assay, *STELA* Single telomeric length analysis, *FISH* Fluorescence in situ hybridization, *SBB* Sudan Black B, *ELISA* Enzyme-linked immunosorbent assay, *CLIAs* Chemiluminescent immunoassays

which suppress the expression of tumor suppressors like $p16^{INK4a}$ and p14. These findings suggest that p21 may play a role in allowing tumor cells to escape senescence, providing a potential mechanism for cancer cell survival and proliferation [18].

In addition to the reversibility of individual cell senescence, the potential reversibility of entire senescent cell populations is also a significant concern. Cellular senescence is not confined to cells under severe stress; it can also affect neighboring cells through the secretion of SASP. Studies have shown that SASP plays a crucial role in maintaining tissue homeostasis by preventing the loss of entire tissue regions when cells are exposed to stressors that induce cell death or senescence [3]. In the context of tumors, senescent cells can contribute to a more aggressive growth phenotype in neighboring cells through SASP signaling [174]. The reversibility of these senescent cell populations is closely linked to tumor growth, recurrence, and drug resistance [175]. Therefore, the development of targeted therapies aimed at eliminating senescent cells represents a promising therapeutic strategy.

Heterogeneity of cellular senescence

The heterogeneity of cellular senescence implies that different cells exhibit distinct features, mechanisms, and outcomes during the process of senescence [176, 177]. Even within the same cell type, variability exists in the onset, progression, manifestation, and response to therapy [178]. As previously mentioned, the factors inducing cellular senescence can be classified into environmental and host factors, and the pathways involved in senescence, such as ATR-CHK1, p53-p21, and $p16^{INK4a}$-CDK4/6, may also vary. The specific manifestations of heterogeneity of senescence are primarily reflected in the characteristics of the SASP [179]. The types and secretion levels of SASP factors vary between different cells and tissues. The factors can be influenced by the type of senescence and its inducing factors. Additionally, the composition of the SASP can change at different stages of the senescence process [170]. In the tumor microenvironment, this heterogeneity is particularly pronounced. We will describe in detail below that senescent cells have a dual role in tumorigenesis and progression. Senescent tumor cells can secrete both pro-inflammatory cytokines, such as IL-6, IL-8, and TNF-α, as well as immunosuppressive factors like IL-10, TNF-β, and VEGF [66]. They can exert anti-tumor effects by inhibiting tumor growth, but may also contribute to tumor progression by promoting adverse outcomes such as metastasis and drug resistance [44, 178, 180]. Therefore, understanding the role of senescent cells and their SASP factors in tumors, particularly across different tumor types and therapeutic contexts, is crucial for the development of novel and more effective therapeutic strategies [181].

Epigenetic regulation of cellular senescence

Epigenetic modifications to DNA and chromatin, such as DNA methylation, histone modifications, and chromatin remodeling, are key regulators of genome architecture and gene expression [182]. These modifications are

crucial in controlling cellular senescence by influencing the expression of senescence-associated genes and the secretion of SASP factors [183].

Cytosine residues in the promoter regions of genes can undergo methylation to form 5-methylcytosine, typically leading to gene silencing. This repression can either promote or inhibit cellular senescence, depending on the specific genes involved. For instance, Oroxylin A has been demonstrated to inhibit cGAS gene methylation by reducing DNMT3A activity, thereby enhancing the cGAS-STING pathway and promoting cellular senescence [184]. Conversely, treatment with telomerase activator compounds (TAC) can stimulate DNMT3B-mediated methylation of the $p16^{INK4a}$ promoter, thus suppressing cellular senescence [141]. Additionally, DNA methylation analysis methods can be used to predict the biological age of individual cells [185].

Recent findings have highlighted that the chemical modifications (e.g., acetylation, methylation, phosphorylation) of histones can alter chromatin structure, thereby influencing gene expression. For example, histone modifications such as H3K9me3 and H3K27me3 contribute to the formation of the senescence-associated heterochromatin foci (SAHF), which silence proliferation-related genes and reinforce the senescent state. Additionally, the transcription factor ZBP-89 and histone deacetylase 3 bind to the $p16^{INK4a}$ promoter, regulating its expression via histone acetylation and consequently influencing cellular senescence [186, 187].

Chromatin remodeling complexes, such as SWI/SNF, ISWI, NuRD, and INO80, can modify chromatin structure by sliding, rearranging, or removing nucleosomes [188]. This modification renders DNA more accessible to transcription factors and other regulatory proteins, thereby promoting gene expression, or alternatively, tightly packaging DNA to suppress gene expression. The long non-coding RNA JPX (just proximal to XIST) interacts with components of chromatin remodeling complexes, such as p65 and BRD4, enhancing the transcription of SASP genes and facilitating cellular senescence [189].

Together, these dynamic epigenetic mechanisms underscore the central role of epigenetic regulation in controlling the cellular senescence program.

Cellular senescence and tumor

Cancer cells are characterized by their ability to proliferate indefinitely, circumvent regulatory controls, and evade programmed cell death, contributing to their prolonged survival. In contrast, senescent cells lose the ability to divide and enter a state of permanent growth arrest. Oncogene-induced cellular senescence is a critical barrier to the malignant progression of human tumors. It induces DNA replication stress and activates DDR, leading to cell cycle arrest during the early stages of tumorigenesis [81, 190]. It has been demonstrated that cellular senescence can limit in vivo tumorigenesis through the p53 and $p16^{INK4a}$ pathways [14, 191]. Additionally, senescent cells are frequently observed in precancerous tumor tissue [192]. Therefore, cellular senescence is typically viewed as a detrimental factor in tumor development and progression. However, emerging evidence indicates that senescent cells can also promote malignant behavior in cancers.

Tumor-associated senescence regulators

Although intracellular oncogenes can induce cellular senescence due to replication stress, research has shown that tumor cells have developed multiple mechanisms to inhibit this process. These adaptations allow tumor cells to evade senescence, enabling them to continue proliferating (Table 2).

A series of studies has demonstrated that specific signaling molecules inhibit cancer cell senescence in various cancer models by directly modulating the p53-p21 and $p16^{INK4a}$ pathways. Sirtuins, a family of NAD^+-dependent deacetylases, play a crucial role in regulating various biological processes, including senescence, metabolism, oxidative stress, and inflammation [249, 250]. Recent studies show that upregulation of SIRT1, induced by estrogen receptor α (ERα) in breast cancer, leads to the inactivation of p53 and cyclin G2, thereby inhibiting senescence and promoting cell survival [196]. Synaptotagmin-7 (SYT7) is upregulated in lung cancer, which augments the interaction between p53 and MDM2, subsequently downregulating the expression levels of p53, p21, and $p16^{INK4a}$, thereby shutting down the senescence program [202]. Similarly, the serine/threonine protein kinase NEK6 [201], the deubiquitinase PSMD7 [203], and casein kinase 2 (CK2) [204] all exhibit inhibition of p53 activity, thereby blocking senescence in lung cancer cells. In lung adenocarcinoma cells, the deletion of IKKα leads to decreased levels of NRF2 and NQO1, which inhibits the p53/p21 pathway and subsequently prevents the induction of senescence [206]. In addition to these factors, the GATA family, comprising GATA1, GATA2, GATA3, GATA4, GATA5, and GATA6, plays a crucial role as essential transcription factors that influence cell proliferation, differentiation, and survival. Specifically, GATA4 and GATA6 exhibit tumor-suppressing functions and are often downregulated in lung cancer. GATA4 facilitates cellular senescence by regulating microRNAs (miRNAs), promoting chromatin remodeling, and activating senescence-associated genes. Meanwhile, GATA6 enhances the expression of p53 and p21, which collectively inhibits its tumor progression [207, 208]. As a critical node in

Table 2 Mechanisms of cellular senescence in cancer

Cancer types	Regulators	Pathways	Effects on cancer	Ref
Breast cancer	$p16^{INK4a}$	$p16^{INK4a}$-CDK4/6	Suppression	[193]
	ΔNp63α	ΔNp63α-HERC3-MM1-c-Myc	Promotion	[194]
	Bmi-1	Bmi-1-$p16^{INK4a}$	Promotion	[195]
	SIRT1	p53-p21	Promotion	[196]
	GATA4	p53-p21	Suppression	[197]
	TRIM27	p53-p21	Promotion	[198]
	Cdc25A	ATM-CHK2	Promotion	[199]
Lung cancer	SK2	SK2-S1P-TERT	Promotion	[200]
	NEK6	p53-p21	Promotion	[201]
	SYT7	p53-p21	Promotion	[202]
	PSMD7	p53-p21	Promotion	[203]
	ZBP-89	$p16^{INK4a}$-CDK4/6	Promotion	[186]
	CK2	p53-p21	Promotion	[204]
	miR-449a	miR-449a-E2F3	Suppression	[205]
	IKKα	p53-p21	Suppression	[206]
	GATA4	WNT7B-GSK3-HIRA-ASF1a	Suppression	[207]
	GATA6	p53-p21	Suppression	[208]
	IRF8	PI3K-AKT	Suppression	[209]
Colorectal cancer	ZEB1	p53-p21 $p16^{INK4a}$-CDK4/6	Promotion	[210]
	FAK	p53-p21	Promotion	[211]
Gastric cancer	FGD5-AS1	p53-p21	Promotion	[212]
	SIRT3	SIRT3-MnSOD-ROS	Promotion	[213]
	PTTG1	p53-p21	Promotion	[214]
	SNHG6	p53-p21	Promotion	[215]
	miR-205-3p	PI3K-AKT	Suppression	[216]
Liver cancer	EZH2	EZH2-miR-139-5p-TOP2A	Promotion	[217]
	AGTR1	p53-p21	Promotion	[218]
	SLC4A11	p53-p21	Promotion	[219]
	DUSP21	p53-p21	Promotion	[220]
	ROC1	p53-p21	Promotion	[221]
	HNRNP A1	$p16^{INK4a}$-CDK4/6	Promotion	[222]
	ASPH	$p16^{INK4a}$-CDK4/6	Promotion	[223]
	TM4SF1	PI3K-AKT	Promotion	[224]
	GCDH	GCDH-PPP-ROS	Suppression	[225]
	NOLC1	p53-p21	Suppression	[226]
	NLRX1	p53-p21	Suppression	[227]
	Let-7i-3p miR-449b-3p miR-624-5p miR-885-5p	Wnt-β-catenin-c-Myc	Suppression	[228]
	miR-138	miR-138-TERT	Suppression	[229]
	miR-125b	miR-125b-SUV39H1	Suppression	[230]
Skin cancer	IGF-1	DNA damage	Suppression	[231]
	JNK2	$p16^{INK4a}$-CDK4/6	Promotion	[232]
	OVAAL	OVAAL-PTBP1-p27	Promotion	[233]
	14–3-3σ	14–3-3σ-CDC25	Suppression	[234]
	Egr1	p53-p21	Suppression	[235]

Table 2 (continued)

Cancer types	Regulators	Pathways	Effects on cancer	Ref
Leukemia	MLL/AF4	MLL/AF4-HOXA7-TERT	Promotion	[236]
	AML/MTG8	AML/MTG8-TERT	Promotion	[236]
	MYCN	MYCN-EZH2-p21	Promotion	[237]
	miR-34c-5p	p53-p21	Suppression	[238]
Glioma	VEGFR2	VEGFR2-AKT-PGC1α-TFAM-mitochondria-ROS	Promotion	[239]
	PRKD2	p53-p21	Promotion	[240]
	CPEB1	p53-p21	Promotion	[241]
	Bcl2L12	p53-p21	Promotion	[242]
	FOXG1	p53-p21	Promotion	[243]
	miR340	p53-p21 $p16^{INK4a}$-CDK4/6	Suppression	[244]
Ovarian cancer	S1PR1	S1PR1-PDK1-LatS1/2-YAP	Promotion	[245]
	SIRT7	SIRT7-GATA4 SIRT7-Wnt	Promotion	[246]
	c-Myc	c-Myc-p27	Promotion	[247]
	ITPKA	p53-p21	Suppression	[248]

the senescence pathway, $p16^{INK4a}$ is often inhibited by cancer-promoting factors. For example, the transcription factor ZBP-89 epigenetically represses $p16^{INK4a}$ expression, preventing senescence in lung cancer cells [186]. Similarly, the enzyme aspartate β-hydroxylase (ASPH) is overexpressed in HCC. Inhibition of ASPH expression and activity leads to the inactivation of GSK3β, promoting stabilization of $p16^{INK4a}$ and inducing senescence [223]. In the context of colorectal cancer, ZEB1 promotes tumor growth by activating DKK1, mutant p53, Mdm2, and CtBP, while simultaneously inhibiting p53-mediated senescence and apoptosis. Moreover, ZEB1 suppresses senescence-related genes such as $p16^{INK4a}$ and p21, contributing to the aggressive nature of the tumor [210].

Under normal conditions, oxidative stress can trigger cellular senescence, leading to growth arrest. However, cancer cells boost their tolerance to oxidative damage, enabling them to evade this process and keep proliferating. Compared to normal gastric epithelial cells, the expression of SIRT3 is significantly elevated in gastric cancer cells. SIRT3 enhances the activity of MnSOD, protecting cells from oxidative damage, which confers strong anti-senescence properties [213]. In glioblastoma, VEGFR2 has been found to suppress cell progression by inducing OSIS through the AKT-PGC1α-TFAM mitochondrial biogenesis signaling cascade [239].

RS, one of the important mechanisms underlying cellular senescence, is often suppressed in various cancer cells. Sphingosine kinase 2 (SK2) has been reported to produce sphingosine-1-phosphate (S1P), which binds to TERT, assisting in telomerase stabilization and thus inhibiting senescence while sustaining tumor growth [200]. In infant acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), fusion oncogenes such as MLL/AF4 and AML/MTG8 are frequently activated. These genes are critical for maintaining telomerase activity, and inhibiting their expression can downregulate TERT and induce cellular senescence [236].

Non-coding RNAs (ncRNAs) also play critical roles in regulating cellular senescence in cancers. Compared to normal liver tissues, levels of ncRNAs such as Let-7i-3p, miR-449b-3p, miR-624-5p, miR-885-5p, miR-138, and miR-125b are significantly reduced in tumors. These miRNAs suppress cell proliferation and induce senescence by modulating downstream pathways, including inhibition of Wnt/β-catenin signaling, downregulation of TERT expression, and suppression of SUV39H1 [228–230]. miR-449a inhibits E2F3 activity, blocking the G1/S phase transition, and its expression is significantly reduced in lung cancer tissues [228].

Cancer-promoting functions of cellular senescence

While the suppression of cellular senescence acts as a protective mechanism in tumorigenesis and progression, senescent cells may also exert beneficial effects within this context. Premature senescence in normal cells may increase the risk of tumorigenesis [251–253]. For instance, the restoration of mammary cell viability by the drug TPCA-1 significantly reduces the incidence of age-related cancers [254]. Similarly, skin cells exposed to ultraviolet radiation age more rapidly and demonstrate a

significantly higher risk of developing skin cancer. In this context, the accumulation of senescent cells and SASP may accelerate the progression of cutaneous squamous cell carcinoma (cSCC) [255, 256]. This increased cancer risk may be associated with factors such as telomere shortening, accumulation of genetic and epigenetic alterations, and reduced DNA repair capacity [257].

An increasing body of evidence suggests that SASP plays an important role in mediating both pro-tumorigenic and anti-tumorigenic effects in cancer progression. Components of the SASP contribute to the establishment of a pro-inflammatory and immunosuppressive microenvironment that facilitates the growth of cancer cells. For example, senescent hepatic stellate cells contribute to chronic inflammation in the tumor microenvironment (TME) by secreting IL-1β, thereby facilitating the progression from non-alcoholic steatohepatitis (NASH) to liver cancer [44, 258]. Similarly, senescent cells can secrete IL-33 to stimulate the recruitment of immunosuppressive cells such as Tregs, further promoting tumor growth through immune suppression [259]. Additionally, SASP can drive tumor invasion and metastasis. For example, senescent glioma cells promote invasion through the secretion of cathepsin B [260], while senescent colon cancer cells induce epithelial-mesenchymal transition (EMT) in surrounding cells via IL-6, MMP-3, fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) [261]. Conversely, the SASP exerts antitumor effects. In the early stages of liver carcinogenesis, IL-1β and TNF-α activate a "senescence surveillance" mechanism that recruits immune cells, including natural killer cells and macrophages, to eliminate potential cancerous cells [262].

Harnessing cellular senescence for cancer therapy

Cellular senescence plays a dual role in cancer development, making it a promising target for anticancer therapy [263]. Several treatments—including targeted therapies, chemotherapy, radiotherapy, and traditional Chinese medicine (TCM) —aim to inhibit tumor growth and metastasis by inducing senescence in tumor cells. However, senescence in immune cells within the TME can weaken antitumor immunity and promote cancer progression, underscoring the importance of anti-senescence strategies. This review will summarize the mechanisms involved in targeting cellular senescence in anticancer therapies.

Targeted therapy

Tumor-targeted therapy is an innovative approach to cancer treatment that aims to inhibit the growth and spread of cancer cells while minimizing damage to normal cells and reducing side effects by targeting specific molecular or genetic pathways. The mechanism of senescence inducers aligns with this concept, as they drive cancer cells into a state of senescence, halting their proliferation [264]. This positions senescence inducers as a novel class of tumor-targeted therapies. In the following section, we will explore the mechanisms and efficacy of different senescence inducers (Table 3).

Telomere shortening is a crucial factor in cell senescence. In many cancers, elevated telomerase expression and activity enable cancer cells to maintain telomere length and evade senescence. To counter this, several telomerase-targeted therapies aim to induce senescence in tumor cells by promoting telomere shortening. Atorvastatin, commonly used to lower cholesterol, inhibits the IL-6/STAT3 signaling pathway, thereby reducing TERT expression and inducing G0/G1 phase cell cycle arrest, ultimately suppressing the proliferation of hepatocellular carcinoma (HCC) cells [265]. Additionally, the TTAGGG repeat sequence at the 3' end of telomeric DNA can form G-quadruplex structures through G-G pairing, which prevents telomerase from binding and elongating telomeres. G-quadruplex-stabilizing ligands, such as perylene and phenyl-imidazole-ethylamine-platinum (II) (PIP), promote the formation of these structures, inhibit telomerase activity, and suppress cell proliferation [269, 270]. Bone morphogenetic protein-7 (BMP7) inhibits TERT activity via the BMPRII receptor and SMAD3 pathway, leading to telomere shortening in breast cancer cells [271]. Moreover, shelterin complexes play a crucial role in regulating telomere length. For example, the aflatoxin B derivative FKB04 induces senescence in liver cancer cells by inhibiting the expression of telomeric repeat-binding factor 2 (TRF2), disrupting the T-loop structure, shortening telomeres, and ultimately leading to cellular senescence [266].

ROS accumulation is a key trigger of cellular senescence and is often targeted by senescence inducers. Resveratrol enhances ROS generation through the SIRT1/p38MAPK and NO/dLC1 pathways by increasing the expression of tumor suppressor gene DLC1, triggering ER stress, and depleting intracellular antioxidants. Additionally, it increases the expression of DNA double-strand break marker γ-H2AX and decreases the levels of DNA repair proteins p-BRCA1 and RAD51, ultimately promoting SA-β-gal activity and the expression of senescence markers p53, p21, and LaminB [272–274]. Some studies show that leukemia can be effectively combated by inducing tumor cells into senescence. Imidazo[1,2-a] pyridines (IPs) enhance lipid peroxidation and reduce GSH levels [277], while curcumin analog pentachloropropane-1 (PGV-1) competes with GSH for binding to GST-P1, inhibiting ROS scavenger enzyme activity [278].

Table 3 Overview of compounds for targeting cellular senescence in cancer

Compounds	Targeted strategies	Cancer types	Ref
Atorvastatin	Telomere	Hepatocellular carcinoma	[265]
FKB04	Telomere	Liver cancer	[266]
6-paradol and 6-shogaol	Telomere	Lung cancer	[267]
AZT	Telomere	Breast cancer	[268]
Perylene	Telomere	Lung cancer	[269]
PIP	Telomere	Lung cancer	[270]
BMP7	Telomere	Breast cancer	[271]
Resveratrol	ROS	Breast cancer, liver cancer and lung cancer	[272–274]
AS1041	ROS	Leukemia	[275]
RGS	ROS	Colorectal cancer	[276]
IPs	ROS	Leukemia	[277]
PGV-1	ROS	Leukemia	[278]
AKI603	ROS	Leukemia	[279]
5-azacytidine, 5-aza-2′-deoxycytidine	p53-p21	Hepatoma, colon, renal, and lung cancer	[280]
PAB	p53-p21	Lung cancer	[281]
β-Asarone	p53-p21	Colorectal cancer	[282]
[Pt (en)]2ZL	p53-p21	Gastric cancer	[283]
Cucurbitacin-b + Withanone	p53-p21	Lung cancer	[284]
AURKA + MDM 2 antagonists	p53-p21	Melanoma	[285]
Berberine derivative B68	p53-p21	Colorectal cancer	[286]
LY83583	p21-CDK/Cyclin	Malignant melanoma and breast cancer	[287]
Sodium valproate	p21-CDK/Cyclin	Liver cancer	[288]
Argentatin B	p21-CDK/Cyclin	Colorectal and prostate cancer	[289]
1,25(OH)2D3	p21-CDK/Cyclin	Liver cancer	[290]
Adapalene	p21-CDK/Cyclin	Prostatic cancer	[291]
Carvacrol	p21-CDK/Cyclin	Lung cancer	[292]
Imatinib	p21-CDK/Cyclin	Leukemia	[293]
Abemaciclib	$p16^{INK4a}$-CDK4/6	Liposarcoma	[294]
Palbociclib	$p16^{INK4a}$-CDK4/6	Gastric cancer	[295]
AVN A	p53-p21	Colorectal cancer	[296]

Anthraquinone lactone AS1041 decreases total thiols and disrupts matrix metalloproteases [275], all of which elevate ROS levels and induce senescence in leukemia cells.

In addition to regulating telomere length and ROS levels, targeting key pathways involved in cellular senescence, such as the p53-p21 axis and $p16^{INK4a}$-CDK4/6 axis, has proven to be an effective therapeutic strategy. DNA methyltransferase inhibitors (DNMTis), including 5-azacytidine, 5-aza-2′-deoxycytidine, pseudolaric acid B (PAB), β-Asarone, and the platinum-zoledronate complex [Pt(en)]2ZL, as well as combinations like cucurbitacin B with Withanone and Aurora kinase A (AURKA) inhibitors with MDM2 antagonists, have been shown to activate the p53 pathway, induce cellular senescence, and inhibit cancer cell growth, tumor progression, and metastasis [280–285]. It is noteworthy that some tumors, such as PD-L1-positive senescent tumor cells, can resist immune clearance and relapse after senescence. However, berberine derivative B68 has been shown to induce p53-dependent cellular senescence, disrupt the immunosuppressive PD-1/PD-L1 interaction, and facilitate the rapid clearance of senescent tumor cells [286]. Some drugs can induce cellular senescence by directly activating p21, independent of the p53 pathway. For example, guanylate cyclase inhibitor LY83583 [287], sodium valproate (a known HDAC inhibitor) [288], Argentatin B [289], 1,25(OH)2D3 [290], adapalene [291] and carvacrol [292] all enhance p21 expression, inhibit CDK and cyclins activity, and induce cellular senescence. The frontline treatment for chronic myeloid leukemia (CML), imatinib, not only induces apoptosis and autophagy but also increases p21 and p27 expression, as well as the population of SA-β-gal-positive cells [293]. Selective CDK4/6 inhibitors have also been proven to be effective senescence inducers [294]. For instance, palbociclib inhibits CDK4/6 activity, while also suppressing proteasome

inhibitor EMC29, leading to proteasome activation and preventing Rb phosphorylation and E2F release, blocking the transition of cancer cells from the G1 to the S phase [295, 297]. It is worth noting that the senescence induced by CDK4/6 inhibitors in tumor cells is partially reversible, which may increase the risk of tumor recurrence, warranting further investigation [298].

miRNAs are small, non-coding RNA molecules that play a crucial role in regulating senescence-related gene expression by binding to messenger RNA (mRNA), thereby preventing its translation or promoting its degradation [299]. Some miRNAs mentioned earlier (such as miR-449b-3p, miR-624-5p, and miR-138) have been shown to promote cellular senescence [228]. However, their expression is often suppressed in tumor cells. Enhancing the expression of these miRNAs is considered a therapeutic approach to induce senescence. Avenanthramide A (AVN A) increases miR-129-3p expression, inhibits the expression of the ubiquitin ligase Pirh2, and upregulates p53 and its downstream target p21, thereby inducing senescence and inhibiting colon cancer growth [296].

Gene therapy plays a significant role in cancer treatment by manipulating genetic pathways related to cellular senescence to inhibit tumor growth. For instance, infection of A549 lung cancer cells with a recombinant adenovirus carrying the $p16^{INK4a}$ gene leads to high-level expression of the $p16^{INK4a}$ protein, inhibition of telomerase activity, increased SA-β-gal expression, and significant suppression of cancer cell growth [300]. Furthermore, using CRISPR interference and programmable base editing to correct the −124C > T mutation in the TERT promoter effectively suppresses abnormal TERT overexpression, thereby inhibiting the growth of gliomas harboring this mutation [301]. Additionally, knocking down the gastrin-releasing peptide receptor elevates p53, p21, and $p16^{INK4a}$ levels, activates the epidermal growth factor receptor (EGFR), and reduces p38MAPK levels, leading to increased cell size and cell cycle dynamics consistent with cellular senescence [302].

Chemotherapy and radiotherapy

As early as 2003, studies demonstrated that chemotherapy can induce premature senescence in tumor cells, thereby inhibiting tumor growth [303]. For example, doxorubicin has been shown to upregulate the expression of the growth factor BMP4, which subsequently activates the SMAD pathway to increase the expression of $p16^{INK4a}$ and p21, inducing premature senescence in lung cancer cells [304]. Moreover, combining senescence inducers with chemotherapeutic agents can reduce chemotherapy resistance and increase tumor cell sensitivity to treatment. In colon cancer models, citrate, by promoting excessive lipid biosynthesis in tumor cells and disrupting lipid metabolism, may initiate ATM-mediated senescence pathways, thereby enhancing the inhibitory effect of standard chemotherapy on tumor growth [305]. Norcantharidin (NCTD) has been found to enhance chemotherapy in triple-negative breast cancer (TNBC) by inducing cell senescence and cell cycle arrest through the inhibition of phosphorylated Akt and ERK1/2, as well as the upregulation of p21 and $p16^{INK4a}$ [306]. Inhibitors of DNA-dependent protein kinase (DNA-PK), such as the novel inhibitor M3814, enhance chemotherapy's antitumor effects by reducing DNA repair and inducing a p53-dependent senescence pathway [307].

However, other studies suggest that senescence of tumor cells can contribute to enhance the resistance of tumor tissues to chemotherapy. In colon cancer, senescent cells enhance tumor resistance by upregulating INHBA expression, which negatively regulates the Hippo signaling pathway and inhibits apoptosis [308]. In melanoma, cisplatin has shown limited efficacy, possibly due to senescent melanoma cells activating the ERK1/2-RSK1 pathway through SASP factors, promoting the proliferation of non-senescent cells [309]. In addition, chemotherapy can also lead to immune cell senescence and promote tumor recurrence [310].

As previously mentioned, ionizing radiation is a significant inducer of cellular senescence. Therefore, radiotherapy can induce senescence in tumor cells. Ionizing radiation can upregulate the expression of the E3 ligase TRIM22 in hepatocellular carcinoma cells, triggering senescence by degrading the AKT phosphatase PHLPP2 and activating the AKT-p53-p21 pathway [311]. Senescence inducers have been demonstrated to enhance the antitumor efficacy of radiotherapy. PARP inhibitors, for instance, can further inhibit DSB repair, promoting senescence in breast cancer cells and enhancing the effects of radiotherapy [312]. Lipoic acid has been shown to synergize with radiation to induce death and senescence in breast cancer cells by increasing p53 expression, activating p38MAPK and NF-κB, and causing G2/M cell cycle arrest [313]. BIBR1532 inhibits telomerase and increases radiation-induced telomere dysfunction, leading to chromosomal instability and inhibition of the ATM/CHK1 pathway, impairing DNA damage repair and ultimately increasing radiosensitivity in non-small cell lung cancer (NSCLC) [314].

Traditional Chinese medicine

In recent years, as research into the pharmacological effects of TCM has deepened, an increasing number of TCM components and derivatives have been found to exhibit antitumor activity, demonstrating great potential in cancer prevention, treatment, and adjuvant therapy

[315]. Many TCM compounds and their derivatives, such as andrographolide [316], artemisinin [317], oridonin [318, 319], and curcumin [320], can induce cellular senescence in cancer cells by enhancing the p53/p21 signaling pathway and SA-β-gal activity, making them promising candidates for antitumor therapy. The alkaloid matrine, derived from the plant Sophora flavescens, and Ligustrum lucidum fruit extract (LLFE) induce G0/G1 phase arrest and senescence in liver cancer cells by upregulating p21 and downregulating Rb phosphorylation [321, 322]. Additionally, certain compounds extracted from traditional Chinese medicinal herbs can induce senescence through oxidative stress. For example, curcumin analog CCA-1.1 and pentachloropropenone PGV-1 selectively induce G2/M phase arrest and OSIS in colorectal cancer cells [323], while Platycodin D2 (PD2), extracted from Platycodon, promotes mitophagy in liver cancer cells via NIX, leading to ROS production and activation of the p21-CDK2 pathway to induce senescence [324]. Interestingly, curcumin's anti-cellular senescence effect is now widely accepted [325]. Additionally, it has been demonstrated that oridonin suppresses the senescence of normal fibroblasts by inhibiting AKT signaling [326]. These findings suggest that the dual role of these compounds in regulating senescence may vary depending on the dose and the specific cell type involved.

Tumor interventions related to the TME

The TME refers to the surrounding environment in which tumor cells reside, including immune cells, fibroblasts, the vascular system, and the extracellular matrix. In recent years, many studies have revealed that the senescent microenvironment plays a significant role in tumorigenesis, progression, and metastasis, providing new insights and therapeutic targets for cancer treatment.

Current research indicates that immune cell senescence within the TME plays a detrimental role in tumor development and progression by facilitating immune suppression and evasion [327]. In certain tumors, senescent T cells (CD57, lacking CD28) accumulate in the TME, resulting in an impaired immune response [328, 329]. This is partly due to dysregulated lipid metabolism and altered phospholipase A2 IVa activity, which result in lipid droplet accumulation in T cells, further compromising their immune function [330]. Senescent macrophages enhance anaerobic glycolysis and promote tumorigenesis by secreting various SASP factors in a paracrine manner, such as Bmp2, Ccl2, Ccl7, Ccl8, Ccl24, Cxcl13, and Il10. Notably, the chemokines CCL7 and CCL24 are particularly involved in enhancing cancer cell invasion and metastasis [331–333]. In response to the adverse effects of immune cell senescence, several studies have proposed new therapeutic targets aimed at mitigating immune dysfunction and enhancing antitumor immunity. Preventing tumor-specific T cell senescence by blocking ATM and MAPK signaling, in combination with anti-PD-L1 checkpoint inhibitors, can synergistically enhance antitumor immunity and improve the efficacy of immunotherapy [328]. Moreover, autologous NK cell infusion has been shown to significantly eliminate senescent T cells and suppress tumor progression [334]. Inhibiting the release of SASP factors from senescent cells can effectively alleviate immunosenescence and enhance tumor resistance [335, 336].

Cancer-associated fibroblasts (CAFs), which are abundant in the TME, play a key role in tumor progression. Substantial evidence suggests that senescent CAFs can enhance treatment resistance in tumor cells. Studies have found that radiotherapy induces CAF senescence, which promotes tumor growth through the secretion of insulin-like growth factor-1 [337]. Additionally, senescent CAFs promote the proliferation of NSCLC cells and enhance their radioresistance via the JAK/STAT pathway [338]. One study observed that pretreatment with quercetin effectively reduced the number of doxorubicin-induced senescent fibroblasts and SASP production, thus reducing their pro-tumorigenic effects on osteosarcoma cells [339].

The role of endothelial cell senescence in the TME is primarily related tumor growth, metastasis and spread. Senescent endothelial cells can loosen intercellular junctions, facilitating the spread of tumor cells through the endothelial barrier [340], while also secreting IL-6, which promotes chemotherapy resistance [341]. Interestingly, the tumor suppressor miR-34a induces endothelial progenitor cell (EPC) senescence by inhibiting SIRT1, thereby reducing EPC-mediated angiogenesis and ultimately suppressing tumor growth [342]. Senescent endothelial cells can also promote immune-mediated senescence surveillance through SASP secretion and NF-κB regulation, potentially preventing tumor formation [343].

Senolytics and senostatics

Notably, therapeutic strategies as mentioned above that induce tumor cells senescence may not always be ideal, as senescent cells can promote tumor progression, metastasis, and drug resistance through the secretion of SASP factors and the reversible nature of senescence, especially if they persist for a prolonged period. As a result, inhibiting or eliminating senescent cells is a promising complementary approach to overcoming these challenges, potentially improving therapeutic outcomes and reducing adverse effects associated with prolonged senescence [344].

Senolytics are a class of compounds designed to selectively eliminate senescent cells. These agents reduce the negative effects of senescent cells by specifically targeting BCL-2 family proteins and the p53 pathway to induce programmed cell death in senescent cells [345, 346]. Representative senolytic drugs, such as dasatinib [347] and quercetin [348], exhibit stronger activity in eliminating senescent cells when used in combination [17]. Additionally, when combined with cisplatin and other chemotherapeutic agents, senolytics can potentiate the anti-tumor effects of these treatments [349]. It is important to note that senolytic therapies may have certain toxic side effects under specific conditions, including gastrointestinal toxicity, thrombocytopenia, and the potential to promote tumorigenesis [350–352]. These risks highlight the need for further investigation to better understand their safety profile.

Senostatics are another class of drugs designed to target senescent cells. Unlike senolytics, which directly eliminate senescent cells, senostatics inhibit the activity of senescent cells or their SASP [353]. Senostatics can be classified into three categories based on their mechanisms: inhibitors of SASP, blocking antibodies, and inducers of SASP reprogramming [354]. SASP inhibitors, which are numerous, reduce the secretion of IL-6, IL-8, and TGF-β by inhibiting NF-κB and mTOR, thereby alleviating their negative impact on surrounding tissues and the tumor microenvironment [355, 356]. Blocking antibodies, including various neutralizing antibodies against SASP components or their receptors, such as those targeting IL-11, have been shown to reduce cellular senescence and improve organ function [357]. Inducers of SASP reprogramming can convert pro-inflammatory SASP into a pro-immune phenotype, thereby enhancing antitumor effects. For example, a combination of palbociclib (a CDK4/6 inhibitor) and trametinib (a MEK inhibitor) promotes the secretion of TNF-α and ICAM-1 by senescent cells, which in turn stimulates the NK cell immune response [358].

Despite their promising potential, senotherapies face several challenges, including enhancing specificity, mitigating long-term adverse effects, and overcoming senescent cell heterogeneity [354, 359]. To address these challenges more effectively, emerging evidence suggests that combining senescence inducers, senolytics, and senostatics may enhance therapeutic efficacy compared to using them individually [360]. Recent findings show that ferroptosis inducers or Fe (II)-activated prodrugs can selectively trigger apoptosis in both primary and paracrine senescent cells, reducing cytotoxicity in an Fe (II)-dependent manner [361]. Furthermore, various studies have explored ways to improve the specificity and reduce the side effects of senolytics and senostatics by developing specific delivery systems [362, 363]. For instance, the high lysosomal β-galactosidase activity in senescent cells has been exploited to design delivery systems using galactooligosaccharide-coated drugs [364–366]; the lipofuscin accumulation in senescent cells has been utilized to develop micelle nanocarriers that bind to lipofuscin [367], allowing for more precise targeting of senescent tumor cells and enhancing the anti-tumor effect.

Summary and outlook

In conclusion, cellular senescence plays a dual role in tumor development and progression, functioning as both a tumor suppressor and promoter, with its effects shaped by the heterogeneity of senescence. This complexity necessitates a deeper understanding of the mechanisms underlying senescence and its context-dependent effects within the TME. Future research should focus on elucidating these intricate pathways, particularly the specific contributions of SASP components in various tumor contexts. Developing targeted therapies that modulate SASP could enhance efficacy while minimizing off-target effects, especially in metastatic cancers [368]. Additionally, since senescent tumor cells may impact the efficacy of senescence-inducing therapies due to their reversibility, it is crucial to understand the mechanisms underlying this process. At the same time, optimizing combinations of senescence-inducing therapeutic strategies with senolytics and senostatics is crucial for achieving an optimal therapeutic balance that maximizes benefits while minimizing side effects [369]. Finally, identifying reliable senescence biomarkers to predict treatment response and monitor therapeutic efficacy could facilitate more precise and personalized treatment approaches. Addressing these challenges could significantly advance the clinical impact of senescence-targeted therapies in oncology.

Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASPH	Aspartate β-hydroxylase
ATM	Ataxia-telangiectasia mutated kinase
ATR	Ataxia-telangiectasia and Rad3-related protein
AURKA	Aurora kinase A
AVN A	Avenanthramide A
BMP7	Bone morphogenetic protein-7
CAFs	Cancer-associated fibroblasts
CBD	Cannabidiol
CDKs	Cyclin-dependent kinases
cGAS	Cyclic GMP-AMP synthase
CK2	Casein kinase 2
CML	Chronic myeloid leukemia
COVID-19	Coronavirus disease 2019
cSCC	Cutaneous squamous cell carcinoma
DDR	DNA damage response
DNA-PK	DNA-dependent protein kinase
DNMTis	DNA methyltransferase inhibitors

DSBs	Double-strand breaks
EGFR	Epidermal growth factor receptor
EMT	Epithelial-mesenchymal transition
EPC	Endothelial progenitor cell
ER	Endoplasmic reticulum
ERα	Estrogen receptor α
ETC	Electron transport chain
EZH2	Enhancer of zeste homolog 2
FGF	Fibroblast growth factor
GSH	Glutathione
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
IPs	Imidazo[1,2-a]pyridines
LKB1	Liver kinase B1
LLFE	Ligustrum lucidum fruit extract
LPS	Lipopolysaccharide
LSECs	Liver sinusoidal endothelial cells
miRNAs	MicroRNAs
MMPs	Matrix metalloproteinases
MRN	Mre11-Rad50-Nbs1
mRNA	Messenger RNA
NASH	Non-alcoholic steatohepatitis
ncRNAs	Non-coding RNAs
NCTD	Norcantharidin
NOXs	NADPH oxidases
NPs	Nanoparticles
NSCLC	Non-small cell lung cancer
OIS	Oncogene-induced senescence
OSIS	Oxidative stress-induced senescence
p38MAPK	p38 mitogen-activated protein kinase
PAB	Pseudolaric acid B
PCNA	Proliferating cell nuclear antigen
PD2	Platycodin D2
PGV-1	Pentachloropropane-1
PIP	Phenyl-imidazole-ethylamine-platinum
PM	Particulate matter
PRR	Pattern recognition receptor
PS	Paracrine senescence
qPCR	Quantitative polymerase chain reaction
RB	Retinoblastoma protein
ROS	Reactive oxygen species
RPA	Replication protein A
RS	Replicative senescence
S1P	Sphingosine-1-phosphate
SAHF	Senescence-associated heterochromatin foci
SASP	Senescence-associated secretory phenotype
SA-β-gal	Senescence-associated β-galactosidase
SBB	Sudan Black B
SIRT1	Sirtuin 1
SK2	Sphingosine kinase 2
Sp1	Specificity Protein 1
SSBs	Single-strand breaks
STING	Stimulator of interferon genes
SYT7	Synaptotagmin-7
TAC	Telomerase activator compound
TCM	Traditional Chinese medicine
TERC	Telomerase RNA component
TERT	Telomerase reverse transcriptase
TIS	Therapy-induced senescence
TME	Tumor microenvironment
TNBC	Triple-negative breast cancer
TOPBP1	Topoisomerase-binding protein 1
TPP1	Telomere protection protein 1
TRF2	Telomeric repeat-binding factor 2
UPM	Urban particulate matter
USP15	Ubiquitin-specific protease 15
ZnO	Zinc oxide

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Authors' contributions
CQ, ZWX, SRH and PL provided funding support and contributed to conceive, design, revision and oversight of the manuscript sections. BWL and ZGP wrote and revised the manuscript, designed the figures, and created the tables. HZ, NZ, and ZQL revised the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.
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Declarations

Ethics approval and consent to participate
Not applicable.

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