The role of senescence, its therapeutic relevance and clinical implications in the tumor microenvironment

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Abstract

Cellular senescence is characterized by cell cycle arrest, resistance to apoptosis, the expression of senescence markers, and the acquisition of senescence-associated secretory phenotype (SASP). In this review, we discuss the role of cellular senescence within the tumor microenvironment. Some senescent innate immune cells fail to sustain their antitumor function and may even promote tumor progression. Senescent $CD8^+$ and $CD4^+$ T cells become dysfunctional and are implicated in immunosuppression, angiogenesis, and resistance to immunotherapy. Research on stromal senescence primarily focuses on the SASP. The SASP functions as a double-edged sword. It promotes immune surveillance in the early stages of a tumor while inhibiting tumor immunity in its advanced stages. Strategies to target senescence in cancer therapies include four main approaches: inducing senescence, inhibiting tumor-promoting SASP, clearing senescent cells, and reversing senescence. Although not yet in clinical practice, these approaches hold promise for future cancer treatments.

Keywords: Cellular Senescence, Aging, Tumor Microenvironment, Senescence-associated Secretory Phenotype, Cancer Treatment

1. Introduction

Aging is an inevitable biological process that all humans experience. Given the global impact of aging, advancing research into aging and age-related diseases is crucial. Numerous studies widely acknowledge that cancer is associated with age, demonstrating increased susceptibility among older individuals [1]. Indeed, the hallmarks of aging and cancer share remarkable similarities. Kroemer *et al.* have identified meta-hallmarks common to both aging and cancer, including genomic instability, epigenetic alterations, dysbiosis, and chronic inflammation [2]. Cellular senescence was first described in the 1960s when human fibroblasts exhibited a decline in proliferative capacity after numerous cell cycles in vitro [3]. Arne N Akbar and Sian M Henson have outlined the three phases of senescence induction: induction by stimuli, DNA damage response, and growth arrest [4]. In 2022, Douglas Hanahan introduced four new hallmarks to the previously established ten hallmarks of cancers [5], including the presence of senescent cells [6]. This underscores the critical importance of research on cellular senescence within the TME.

Table 1: Types of senescence and their roles within the tumor microenvironment

Type of senescence	Triggers	Role in TME	Mechanism	Senescent cell	Ref.
TIS	Chemotherapy Radiotherapy Targeted therapy	Anti-tumor	Immune surveillance by NK cells and macrophages	Tumor cell	[7-9]
			Complement activation	Tumor cell	[10]
			Recruitment of DCs and T cells	Tumor cell	[7, 9]
			Sensitization of chemotherapy and ICB in PDAC	Tumor cell	[11]
		Pro-tumor	Metastasis promotion	Tumor cell	[8, 12, 13]

				Fibroblast EC	
			Invasion promotion	EC	[12]
			Stemness induction	Tumor cell	[8]
			Immunosuppression	$CD8^+$ T cell Fibroblast	[14-16]
			Chemoresistance and EMT	Neutrophil Fibroblast	[8, 17]
			ICB resistance	Macrophage $CD8^+$ T cell	[18, 19]
OIS	Oncogene activation	Anti-tumor	Recruitment of $CD4^+$ T cells	Tumor cell EC	[8, 20, 21]
			Macrophage polarization towards M1	Fibroblast	[22]
		Pro-tumor	Tumorigenesis promotion	Macrophage Fibroblast	[8, 23]
			Metastasis promotion	Tumor cell EC	[8, 13]
			Invasion promotion	Tumor cell	[8]
			Chemoresistance	Tumor cell	[8]
			Immunosuppression	Fibroblast	[8]
SIPS	Stress signals	Pro-tumor	Tumorigenesis promotion(x2)	Fibroblast	[24, 25]
			Immunosuppression	Tumor cell	[26]
RS	Shortened telomere length	Pro-tumor	Angiogenesis	EC	[27, 28]
			Tumorigenesis promotion	Fibroblast	[29]
			Impaired immune surveillance	$CD8^+$ T cell	[30, 31]
		Anti-tumor	Growth arrest	Tumor cell	[32]
Age-related immune dysfunction	Physiological aging	Pro-tumor	Macrophage polarization towards M2	Macrophage	[33, 34]
			Impaired immune surveillance	NK cell	[35]
			Metastasis promotion	Neutrophil	[36]
			Impaired antigen presentation	DC	[37-39]
			ICB adverse events	$CD4^+$ T cell	[40]

59 TIS, therapy-induced senescence; OIS, oncogene-induced senescence; EC, endothelial cell; DC,

dendritic cell; NK cell, natural killer cell; ICB, immune checkpoint blockade; PDAC, pancreatic ductal adenocarcinoma; EMT, epithelial-mesenchymal transition.

The tumor microenvironment (TME) is the habitat in which tumor cells live and proliferate. Beyond neoplastic cells, the TME encompasses a heterogeneous assemblage of innate and adaptive immune populations, cancer-associated fibroblasts, endothelial cells, mesenchymal stromal cells, and resident stem-like cells. Numerous reviews have established the link between the senescence of tumor cells and the onset and progression of cancers [41-45]. Therefore, our work will mainly focus on the senescence of non-cancerous components within the tumor microenvironment. In particular, accumulating evidence highlights the induction of senescence in both immune cells and stromal compartments [46-50]. Senescence exerts multifaceted effects on antitumor immunity. On the one hand, senescent cells secrete chemokines and surface ligands that recruit and activate immune surveillance [7-9]; on the other, senescent immune cells may become dysfunctional. Senescence may assist in evading immune clearance through transient cell-cycle re-entry or the release of immunosuppressive factors, thereby fostering resistance to therapy and adverse clinical outcomes. Deconvoluting this paradox is essential for a better understanding of senescence's dualistic roles within TME. Table 1 summarizes the common inductions of cellular senescence within the TME, their triggers, senescent cells involved, and their roles within TME **(Table 1)**. Here, we review the changes in senescence within innate immunity, adaptive immunity, and stroma. We will elaborate on their contributions to tumor progression and cancer therapies, and the extent to which patients may benefit from targeting senescent cells within TME.

2. Aging, immunosenescence, and cellular senescence

In 2013, Kroemer *et al.* proposed nine molecular hallmarks of aging, with cellular senescence as one of them [51]. This underscores the link between physiological aging and cellular senescence. Cellular senescence denotes a state of permanent proliferative arrest that cells enter following extended in vitro replication or upon exposure to sublethal stressors or oncogenic stimuli [52]. Senescent cells exhibit several characteristics: morphological abnormalities, irreversible cell cycle arrest, apoptosis resistance, expression of senescence markers, mitochondrial dysfunction, metabolic alterations, and the acquisition of senescence-associated secretory phenotype (SASP) [52, 53]. The onset of senescence is triggered by a variety of insults—irreparable DNA damage, telomere attrition, mitochondrial perturbations, metabolic derangements, and oncogene activation—all of which accrue with chronological aging [54]. Consequently, cells subjected either to a finite replicative lifespan or to diverse stressors during organismal aging undergo senescence, which in turn contributes to the pathogenesis of multiple age-related disorders. Specifically, metabolism, mitochondrial function, and senescence are interrelated in a bidirectional manner, each influencing and being influenced by the others. Senescent cells exhibit hallmark metabolic alterations, such as heightened aerobic glycolysis, sustained tricarboxylic acid (TCA) cycle activity, increased glutaminolysis, and lipid accumulation [55, 56]. For example, glycogen overload elevates reactive oxygen species (ROS), precipitating senescence [57], whereas methionine deprivation induces DNA damage–mediated senescence [58]. On the other hand, mitochondrial dysfunction—manifested as reduced respiratory capacity and membrane potential, aberrant organelle biogenesis, and mtDNA mutations—drives

cells into senescence [59].

Senescence resulting from repeated cell divisions is termed replicative senescence (RS) [3], driven by telomere shortening. Stress-induced premature senescence (SIPS) encompasses senescence triggered by stress signals such as oncogene activation, hypoxia, and DNA damage [60-62]. Specifically, cellular senescence induced by treatments such as radiation, conventional chemotherapies, or targeted therapies is termed therapy-induced senescence (TIS) [16, 43, 63]. Senescence induced by the aberrant activation of oncogenic signaling is termed oncogene-induced senescence (OIS) [64]. TIS and OIS are both categorized into SIPS.

Differentiating cellular senescence from immunosenescence is critical, as these interrelated yet distinct phenomena both drive organismal aging and age-related pathology. Cellular senescence denotes a cell-intrinsic, irreversible proliferative arrest, whereas immunosenescence refers to the age-associated, systemic decline of immune competence across both innate and adaptive immunity. Immunosenescence can result from thymic involution, persistent antigen exposure, chronic inflammation, etc. [49, 65-68]. Importantly, cellular senescence of immune cells partly contributes to immunosenescence [48, 49]. Among these factors, thymic involution represents the most prominent and specific change associated with immunosenescence [69, 70]. As individuals age, thymic involution leads to thymic atrophy, reduction in thymocytes, and a decreased output of naïve T cells [69, 70]. Subsequently, older individuals may experience an altered phenotype of peripheral T cells, replicative senescence, and ultimately dysfunction in adaptive immunity [71], potentially leading to a higher

mortality [72]. Concurrently, ‘inflammaging’—a state of sterile, chronic, low-grade inflammation driven predominantly by innate immune cells—both contributes to and is exacerbated by immunosenescence [73]. Some researchers believe that inflammaging is a component of physiological aging. Once influenced by frail gene variants, it may lead to age-related diseases, termed as ‘Second hit theory’ [74]. Some may view inflammaging as the counterpart to immunosenescence [75], with each promoting the other. Although senescent cells potentiate inflammaging via pro-inflammatory SASP factors, they represent only one facet of this multifactorial process, which also encompasses accrual of cellular debris, accumulation of damage-associated molecular patterns (DAMPs), and a decline in proteasomal and autophagic clearance mechanisms [41, 76]. Moreover, immunosenescence will drive systemic aging [77]. Researchers have modeled physiological immunosenescence by knocking out Ercc1, a gene encoding a specific DNA repair protein, to reveal the senescence of non-lymphoid organs [77], highlighting the interaction between immunosenescence and aging.

3. Tumor cell senescence: Friends or foe?

3.1. Senescence and Cancer Prior to Oncogenesis

Aging elevates oncogenic risk through chronic inflammation, genomic instability, dysbiosis, and epigenetic drift [78]. Under genotoxic stress—such as DNA damage or aberrant oncogene activation—normal cells either undergo apoptosis or enter a permanent growth arrest termed senescence, thereby acting as a potent tumor-suppressive barrier [79]. Mitochondrial pyruvate dehydrogenase (PDH) activation acts

as a pivotal metabolic mechanism driving oncogene-induced senescence (OIS), linking enhanced mitochondrial respiration and redox stress to OIS-driven tumor suppression. This indicates the significant role of mitochondrial function in cellular senescence. Moreover, senescent cells propagate senescence to neighboring cells via paracrine SASP factors and juxtacrine signals [44], and are cleared by immune cells, a process called senescence surveillance [44, 45, 80]. For example, pre-malignant hepatocytes undergoing OIS are cleared by macrophages recruited through $CD4^+$ T-cell–derived SASP chemokines, and both $CD4^+$ and $CD8^+$ T cells can mediate senescent-cell clearance [9, 20, 81]. Thus, senescence serves as a physiological barrier to oncogenesis.

With advancing age, two factors conspire to weaken this barrier. First, cells accrue senescence-inducing insults—telomere attrition, oxidative damage, and oncogenic mutations—at a higher frequency [53, 64, 82]. Second, immunosenescence compromises surveillance: macrophage phagocytic capacity wanes, antigen-presenting cell function declines, naïve T-cell output diminishes, and T-cell receptor diversity contracts [48, 75]. As a result, the presence of abundant senescent cells becomes a chronic feature of elderly people. Their chronic SASP secretion fosters a pro-tumor microenvironment by sustaining inflammation, promoting malignant transformation, suppressing immune clearance, and remodeling local stroma [44, 45].

3.2. Senescence and Cancer After Tumor Formation

Within established tumors, therapy-induced senescence (TIS) is prevalent [63]. DNA-damaging chemotherapies and radiotherapy induce senescence in malignant cells [83-85]. TIS was also observed in breast cancer, Ewing sarcoma, and neuroblastoma

following treatment with CDK4/6 inhibitors [86], or in lung cancers and pancreatic cancers following treatment with MEK and CDK4/6 inhibitors [11, 87-90].

Senescent tumor cells do undergo growth arrest comparable to that of normal senescent cells. In various cancer models, senescent tumor cells uniformly exhibit cell-cycle arrest or markedly reduced proliferation [91]. Does this mean that senescence of tumor cells facilitates effective tumor suppression? Indeed, therapy-induced senescent tumor cells can attract NK cells and DCs into tumor sites via the upregulation of MHC-I and IL-15/IL-15RA complex [7, 9]. In lymphoma models with TIS, NK cells accumulate with enhanced response to tumor cells [92]. Similarly, in another metastatic melanoma model with OIS, the senescence-induced infiltration of myeloid cells inhibited tumor growth [93]. Preclinical evidence has also shown that therapy-induced senescent tumor cells induce complement activation and increase C3 expression [10]. It seems that senescence brings hope to tumor suppression.

However, senescent tumor cells may paradoxically fuel disease progression. First, the growth arrest of senescent tumor cells is not stable. The re-entry into the cell cycle of therapy-induced or oncogene-induced senescent tumor cells has been demonstrated in mice and patients with breast cancers, colorectal cancers, and acute myelogenous leukemia [63]. Mechanistically, increasing replication stress and DNA damage leads to genomic instability of oncogene-induced senescent tumor cells, enabling escape from growth arrest through various mutations [94]. Therapy-induced senescent tumor cells, on the other hand, escape from cell-cycle arrest through multiple mechanisms, including metabolic reprogramming, chromatin remodeling, and signaling pathway

198 rewiring [94]. Second, preclinical and clinical observations have suggested that TIS
199 may be detrimental. TIS has been associated with chemotherapy-induced cardiotoxicity,
200 peripheral neuropathy, and ovarian damage in mice [16]. Using four
201 immunohistochemical markers, including lipofuscin, $p16^{INK4a}$, $p21^{WAF1/Cip1}$, and Ki67,
202 researchers have found that the tumoral senescence signature significantly affected
203 overall survival (OS) in 155 NSCLC patients [95]. Single-cell analysis also revealed
204 worse prognosis in patients with higher senescence signature [96]. Third, senescent
205 tumor cells foster an immunosuppressive tumor microenvironment. A higher
206 senescence signature correlates with increased crosstalk between tumor cells and
207 immune cells [96]. This is not only attributed to SASP factors secretion, but also to the
208 metabolic alterations of senescent tumor cells. While senescence-associated secretory
209 phenotype (SASP) factors critically establish a protumoral TME, these will be
210 addressed subsequently. Similar to non-malignant senescent cells, senescent tumor cells
211 exhibit enhanced glycolysis [55]. Such a metabolic shift not only promotes tumor
212 invasion but also exacerbates the Warburg effect, driving lactate accumulation that
213 impairs T cell and macrophage function [55, 97]. Senescent tumor cells further display
214 increased lipid uptake and diminished catabolism [55, 56], alterations
215 that correlate with poorer clinical prognosis and immunotherapy resistance in cancer
216 patients [98, 99]. Cellular senescence additionally heightens tumor cell dependence on
217 glutamine metabolism, facilitating cell cycle re-entry [100, 101]. Notably, myeloid-
218 derived suppressor cells (MDSCs) within the TME acquire mitochondrial DNA
219 (mtDNA) released by senescent tumor cells, reinforcing their immunosuppressive

activity [102]. Collectively, this evidence underscores the therapeutic potential of ablating senescent cells. Consequently, senescence-targeting strategies in oncology broadly fall into two categories: inducing senescence to potentiate immune-mediated clearance or eliminating senescent cells to mitigate their chronic protumoral effects on the TME, which will be discussed in the following section.

4. Innate immunity senescence: From bad to worse?

Innate immunity acts as the first line of defense against pathogens. Recently, interest has grown in the role of innate immune cells within the TME [103, 104]. Our focus will be on their induction, functional and phenotypic changes, and contributions to tumor progression.

4.1. Neutrophils

Neutrophils, pivotal components of the innate immune response, primarily originate from the bone marrow (BM) [105]. Although neutrophils are short-lived, they can undergo senescence with functional consequences. One reason for their prolonged survival is impaired GM-CSF-induced apoptosis [106]. In addition to physiological aging, it has been found that apolipoprotein E (APOE) secreted by tumor cells induces a subset of senescent neutrophils expressing the triggering receptor expressed on myeloid cells 2 (TREM2), which correlates with poor prognosis [107]. Patients with breast cancer receiving chemotherapy harbor highly senescent neutrophils [17]. This indicates that both tumors and cancer therapies can induce the senescence of neutrophils. Neutrophils become dysfunctional in killing microbes. Although neutrophil counts remain stable with age [108, 109], their defense against infection declines [110, 111].

However, this does not necessarily mean that senescent neutrophils are dysfunctional within the TME. We will separately discuss the effects of senescence on the anti-tumor and pro-tumor functions of neutrophils.

Senescent neutrophils are defined as $CXCR4^{+}CD62L^{low}$ neutrophils [36, 112, 113]. Neutrophils can exert antitumoral effects through various mechanisms [114], which can be potentially influenced by senescence. First, neutrophils can kill tumor cells opsonized with IgA or IgG via Fcγ- or Fcα-receptors [115], a process known as antibody-dependent cellular cytotoxicity (ADCC). Diminished Fcγ-mediated ADCC has been observed in senescent human neutrophils in both sexes, resulting from impaired free radical production [116]. However, FcαR1 (CD89) is the principal receptor mediating neutrophil cytotoxicity against cancer cells [117, 118]; therefore, it cannot yet be concluded that the overall ADCC capacity is reduced in senescent neutrophils. Neutrophils also exert antitumoral functions by secreting ROS and neutrophil extracellular traps (NETs) in certain scenarios. These functions will be focused on below. Moreover, neutrophils have been demonstrated to acquire antigen-presenting capabilities, bridging innate and adaptive immunity in lung cancer [119, 120]. Their potential as antigen-presenting cells is further supported by recent profiling [121]. However, further investigation is required to understand the influence of aging on this capacity. Overall, there is not yet sufficient evidence to definitively assess the impact of senescent neutrophils on tumor development. This may be due to the relatively recent association of neutrophils with tumors. Continued efforts are necessary to unravel the complexities surrounding neutrophil senescence.

Neutrophils exert a protumoral effect throughout the development of tumors **(Figure 1A)**. ROS, though observed to kill tumor cells in some research [122], has been

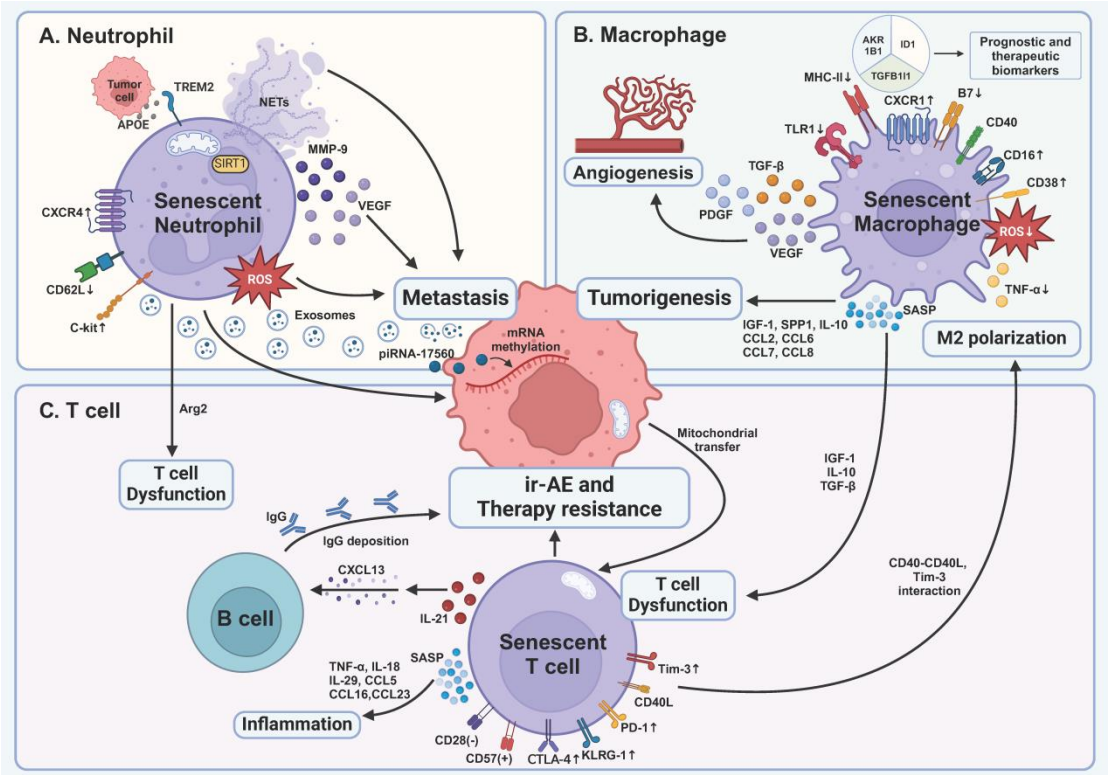

Fig.1 **Impact of senescent immune cells on tumor development and treatment within the tumor microenvironment. A** TREM2-expressing senescent neutrophils are induced by APOE secreted by prostate tumor cells, correlating with a poor prognosis. Senescent neutrophils promote cancer metastasis via distinct pathways, including ROS, mitochondria-dependent NETs, and cytokines. They also produce exosomes containing piRNA-17560, which causes chemotherapy resistance by RNA methylation of tumor cells. Senescent neutrophils lead to T cell dysfunction by Arg2 production. **B** Senescent macrophages' capability of killing tumor cells is inhibited, proven by decreased expression of MHC-II, B7, and impaired production of ROS and TNF-α. Senescent macrophages are another main force of SASP factors, leading to early tumorigenesis, angiogenesis, and immunosuppression. **C** Senescent T cells become dysfunctional as demonstrated by the expression of inhibitory receptors, including PD-1, Tim-3, and CTLA-4, and inhibitory SASP factors produced by senescent macrophages. In turn, senescent T cells enhance M2 polarization through CD40L and Tim-3 interaction. Moreover, senescent T cells secrete SASP factors to cause age-associated inflammation and deteriorate immune cell-related adverse events of ICB via IL-21-CXCL13-B cell-IgG axis. TNF-α, tumor necrosis factor-α; IL, interleukin; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; Tim-3, T cell immunoglobulin and mucin domain-containing protein 3; PD-1, programmed death 1; KLRG-1, killer cell lectin-like receptor subfamily G 1; CXCL, C-X-C motif ligand; CCL, C-C chemokine motif ligand; SASP, senescence-associated secretory phenotype; ir-AE, immune cell-related adverse event; IGF-1, insulin-like growth factor 1; TGF-β, transforming growth factor-β; piRNA, PIWI-interacting RNA; NETs, neutrophil extracellular traps; TREM2, triggering receptor expressed on myeloid cells 2; APOE, apolipoprotein E; Arg2, arginase 2; SIRT1, silent mating type information regulation 2 homolog-1; MMP-9, matrix metallopeptidase 9; VEGF, vascular endothelial growth factor; ROS, reactive oxygen

species; SPP1, secreted phosphoprotein 1; PDGF, platelet derived growth factor; TLR1, Toll-like receptor 1; MHC-II, major histocompatibility complex II. This figure was created with BioRender (https://biorender.com/).

demonstrated to promote chronic inflammation and carcinogenesis via nitric oxide (NO) production [123] and cause severe T cell immunosuppression [124]. Given the elevated ROS levels in the elderly group [125], this increase may further promote tumorigenesis. NETs represent another age-associated mechanism that contributes to tumor promotion. NETs consist of DNA, histones, neutrophil elastase, matrix metalloproteinases, etc. [126]. The impact of NETs on the tumor is complex. Certain components of NETs, including myeloperoxidase and defensins, can directly kill tumor cells [114, 126]. The DNA structure of NETs is capable of capturing tumor cells, thereby preventing tumor metastasis [114]. However, NETs can facilitate tumor proliferation, invasion, angiogenesis, and the formation of immunosuppressive TME [126]. Therefore, it can be hypothesized that impaired NETs function in senescent neutrophils [127] may attenuate the aforementioned process, yet their overall impact on tumor development remains uncertain. Furthermore, neutrophils facilitate tumor metastasis **(Table 1)** [36, 113]. Adoptive transfer of a subset of $CXCR4^{high}CD62L^{low}$ senescent neutrophils promotes tumor metastasis of breast and melanoma cancer cells to the liver [113]. Accumulation of $CXCR4^{+}CD62L^{low}$ senescent neutrophils has also been found in the lung premetastatic niche at early stages of breast cancers, characterized by the expression of a specialized transcription factor SIRT1 [36, 128]. Finally, senescent neutrophils promote resistance to chemotherapy [17]. Senescent neutrophil-derived exosomal piRNA-17560 stimulates the expression of fat mass and

obesity-associated protein (FTO) in breast cancer cells, leading to chemoresistance and epithelial-mesenchymal transition (EMT) [17]. Altogether, neutrophil senescence favors tumor progression, making senescent neutrophils a potential therapeutic target.

Indeed, emerging efforts to target neutrophils in cancer therapy are showing promise [114], although the influence of senescent neutrophils on these therapies remains unclear. Interestingly, researchers have recently trained neutrophils to eliminate tumor cells in a ROS-dependent manner [129], highlighting the ROS's potential in defending against tumors. Though increased levels of ROS have been found in older populations [125], in patients with breast cancers, resistance to chemotherapy has been attributed to senescent neutrophils [17]. The efficacy of such approaches in elderly patients requires further exploration.

4.2. Macrophages

Macrophages are critical TME components, categorized as classically activated M1 macrophages and alternatively activated M2 macrophages based on their activation pathways [130]. M1 macrophages, predominantly antitumoral, are identified by $CD14^{high}CD16^{-}MHC\text{-}II^{high}$ expression, while M2 macrophages, which are protumoral, exhibit $CD14^{low}CD16^{high}$ $MHC\text{-}II^{low}$ expression [130, 131]. Senescent macrophages comprise a heterogeneous subset characterized by elevated CD38 expression [132]. The senescence of macrophages can be induced by tumors. In a glioblastoma model, the 8B cells induced a senescence-like state of macrophages by the production of IL-6 [133], typical components of SASP [8]. This subset of macrophages, similar to M2 macrophages, produced high levels of Arginase-1 and inhibited T cell function within

the TME [133, 134]. Radiotherapy has also been found to induce senescence of myeloid cells in MC38 colon cancer models [19].

M1 macrophages are activated by Th1 cells or IFN-γ and kill tumor cells with mechanisms similar to those employed during infections, including ROS, lysosomal enzymes, and NO. Recruited by $CD4^+$ T cells, M1 macrophages acquire the ability to eliminate pre-malignant senescent hepatocytes [20], thereby preventing tumor initiation. They also serve as antigen-presenting cells (APCs) to activate adaptive immunity. However, the antitumoral capacity of senescent M1 macrophages is compromised in several ways **(Figure 1B)**. Firstly, reductions in $CD14^+CD16^-$ macrophages, representing M1 subsets, have been observed in both aged humans and mouse models in the peripheral blood [33, 34]. Using single-cell techniques, the M2 expansion in aged humans was also supported [135]. In liver models with chronic damage, however, p53-expressing senescent hepatic satellite cells have been proved to polarize M2 subsets into M1 subsets [22], indicating the number of M1 macrophages may be organ-dependent. Secondly, the production of cytokines such as TNF-α, as well as the expression of TLR1, was impaired [33]. The underlying mechanisms remain to be elucidated. Additionally, reduced ROS production in senescent macrophages was observed [8], weakening tumor immune surveillance. Furthermore, decreased expression of MHC-II and B7 costimulators in senescent macrophages indicates a diminished response to vaccination [136, 137]. These findings demonstrate significant impairments in the antitumoral functions of senescent M1 macrophages.

M2 macrophages, driven by Th2 cells or Tregs, promote tumor growth through

various mechanisms **(Figure 1B)**. As previously mentioned, increased M2 subsets are observed in elderly humans and mouse models [33, 34, 135]. The accumulation of senescent macrophages further promotes tumor progression [23, 138]. Prieto *et al.* have found that senescent alveolar macrophages expressing $p16^{INK4a}$ and Cxcr1 increased in the lungs with aging in human and Kras-driven mice models, and their removal attenuated the tumor development [138]. These studies underscore the significant role of senescent macrophages in early tumor initiation. M2 macrophages further promote tumor progression by inhibiting adaptive immunity and NK cells through the production of IL-10, TGF-β, and the expression of PD-L1 [130]. In aged mice, senescent macrophages produce elevated levels of IL-10 in the lungs, further suppressing the IL-12 axis, which is crucial for NK cell functionality [139]. In an MC38 colon cancer model, radiotherapy-induced senescent M2 macrophages were sufficient to inhibit T cell functionality. The clearance of senescent cells reversed the proliferation of T cells, suggesting that senescence may foster an immunosuppressive TME regulated by M2 subsets [19]. Finally, M2 macrophages promote angiogenesis through the production of VEGF, PDGF, and TGF-β [134], although the anti-angiogenic effect of senescent macrophages is compromised by the loss of Fas ligand (FasL) [140]. Overall, these findings suggest that senescence makes macrophages more likely to promote tumor progression.

4.3. MDSCs

Myeloid-derived suppressor cells (MDSCs) comprise a heterogeneous group of myeloid progenitor cells and immature myeloid cells (IMCs) [141]. They are

categorized into monocytic (Mo-MDSCs) and polymorphonuclear MDSCs (PMN-MDSCs) [142], analogous to macrophages and neutrophils, respectively. MDSCs suppress tumor immunity through various mechanisms [141] while aging further enhances these immunosuppressive effects. First, aged mouse models exhibit expanded MDSC populations that produces IL-6 relevant to inflammaging [143-145]. In the bone marrow of aged mice, MDSCs make up the majority of the NF-κB-expressing cells, suggesting NF-κB's role in their increase [145]. Secondly, with aging, SASP factors can enhance the proliferation and functionality of MDSCs [146]. $p16^{Ink4a}$ and $p21^{Cip1/Waf1}$ are highly expressed in Mo-MDSCs and stimulate CX3CR1 chemokine receptor expression, leading to the accumulation of Mo-MDSCs at tumor sites [147]. Third, single-cell analysis revealed that, in the high-senescence-signature group, malignant cells exhibited a greater degree of interaction with MDSCs across many human cancers, indicating an enhanced immunosuppressive capacity of MDSCs [96]. This evidence strongly suggests that aging reinforces the immunosuppressive role of MDSCs.

4.4. NK cells

NK cells are crucial for immune surveillance against cancers, consisting of immature $CD3^{-}CD56^{bright}$ NK cells and mature $CD3^{-}CD56^{dim}$ NK cells, with the latter accounting for the majority [148]. Mature NK cells directly eliminate tumor cells via the production of perforin and granzyme B, or expression of FasL and TNF-related apoptosis-inducing ligand (TRAIL) [148], while immature NK cells contribute to tumor cell elimination by producing cytokines such as IFN-γ, TNF-α, and GM-CSF [149]. Furthermore, NK cells play a critical role in neutralizing senescent cells, thereby

preventing early tumorigenesis [8]. For example, uterine NK cells clear senescent decidual cells following the induction of IL-15 [150]. Senescence impacts both subsets of NK cells. In a study examining changes in aged NK cells, an increase in NK cell numbers with age was observed in 11 out of 13 studies [151]. The absolute number of immature $CD3^{-}CD56^{bright}$ NK cells has been shown to decrease with aging [152-154]. Additionally, the response of NK cells to IL-2 was impaired [152], and their ability to produce IFN-γ and IL-8 was significantly inhibited [155, 156]. In mature $CD3^{-}CD56^{dim}$ NK cells, age-related declines in perforin lead to reduced NK cell cytotoxicity (NKCC) [153]. Additionally, the expression of NK cell activating receptors like NKp30 and NKp46 was reduced in elderly groups [154]. Consistent with the reduction in NKCC, compromised tumor immunosurveillance of senescent NK cells against acute myeloid leukemia has been found [35]. Overall, this evidence suggests that the senescence of NK cells leads to a diminished antitumoral effect.

4.5. Dendritic cells

Dendritic cells (DCs), as the quintessential APCs, play a critical role in bridging innate and adaptive immunity. DCs are classified as conventional DCs (cDC1 and cDC2) or plasmacytoid DCs (pDCs). cDC1 and cDC2 are respectively tasked with antigen presentation to $CD8^{+}$ T cells via MHC-I and $CD4^{+}$ T cells via MHC-II, while pDCs are dedicated to antiviral and antitumor immunity through the production of type I interferons [157]. Aging impacts both cDCs and pDCs through several mechanisms. For cDCs, their absolute number remains unchanged with aging [37], and research has reported a diminished capacity for phagocytosis, migration, and T cell stimulation [37,

38]. In mouse models with B16-ovalbumin (OVA) melanomas, senescent DCs failed to effectively stimulate T cells due to defective CCR7 signaling, despite an unchanged capacity of antigen presentation [38], which led to tumor progression. In aged humans, a decreased expression of MHC peptide and CD40 in cDCs was observed, subsequently impairing $CD4^+$ T cell expansion [39]. In pDCs, impaired production of type I and III interferon has been observed, resulting in reduced $CD8^+$ T cell cytotoxicity [158]. Moreover, NK cells were unable to activate and eradicate lymphoma tumor cells due to a deficiency in IL-15, IL-18, and IFN-α production by pDCs [159]. Therefore, both DC subsets exhibit a functional decline in tumor immunity during aging.

5. Adaptive immunity senescence: The main force of immunosenescence

Adaptive immunity plays a central role in tumor defense, with $CD8^+$ cytotoxic T lymphocytes (CTLs) serving as the primary effector cells. Besides, $CD4^+$ T cells, regulatory T cells (Tregs), and B cells all participate in the interaction of tumors and the TME. Thus, exploring the senescence of adaptive immunity is essential in discussions of immunosenescence and tumor progression. Our focus will primarily be on the role of senescent T cells within the TME, with a brief overview of senescent B cells, whose role in the TME remains less defined.

5.1. $CD8^+$ T and $CD4^+$ T cells

Following cross-presentation and costimulation primarily by cDC1 in secondary lymphoid organs, naïve $CD8^+$ T cells become activated and migrate to tumor sites, where they directly eliminate tumor cells through perforin/granzyme-mediated or FAS/FASL-mediated cytotoxicity. $CD4^+$ T cells, particularly Th1 cells, enhance

449 antitumor immune responses by augmenting $CD8^+$ T cell activity and activating M1
450 macrophages by producing IFN-γ [160]. Like other innate immune cells, both $CD8^+$
451 and $CD4^+$ T cells can eliminate senescent cells [9, 20, 81]. Oncogene-induced pre-
452 malignant senescent hepatocytes were cleared by macrophages, which were recruited
453 by $CD4^+$ T cells through the secretion of SASP [20]. Furthermore, senescent cancer
454 cells are highly immunogenic, facilitating their recognition and elimination by DCs and
455 $CD8^+$ T cells [9]. T cells are crucial in the clearance of senescent cells.

456 T cells are the most extensively studied immune cells in the context of
457 immunosenescence. Multiple pathways contribute to T cell senescence, with p38 and
458 p53 being the most studied [4]. Senescent $CD8^+$ T cells were induced in LCMV-infected
459 mice and aged CMV-infected patients [161, 162], characterized by expression of killer
460 cell lectin-like receptor subfamily G 1 (KLRG-1) and impaired proliferation [162]. TIS
461 is also observed in T cells. In non-small cell lung cancer (NSCLC) patients,
462 chemotherapy induces T cell senescence [163]. Lately, researchers have found that
463 chemoradiotherapy induced senescence of $CD8^+$ T cells in human cervical cancers [14].
464 Mechanistically, concurrent chemoradiotherapy triggers expression of atypical
465 chemokine receptor 2 (ACKR2) on tumor cells, thus increasing the production of TGF-
466 β and driving T cell senescence [14]. Peripheral phospholipids were also responsible
467 for T cell senescence [164]. Furthermore, in various cancers including breast cancers,
468 melanomas, colon cancers, prostate cancers, ovarian cancers and head and neck cancers
469 [165-167], tumor-derived immunoglobulin-like transcript 4 (ILT4) and PD-L1 in EVs
470 reprogrammed lipid metabolism and induced $CD4^+$ T cell senescence via MAPK

ERK1/2 signaling, leading to tumor progression and a poor prognosis [165, 168]. Tumor-T cell contact can activate cAMP pathways to trigger $CD4^+$ T cell senescence, a process reversed by tumor cell TLR8 activation [166]. Recently, emerging evidence indicates that tumor cells further promote T cell senescence via mitochondrial transfer [169]. Mechanistically, T cells internalize tumor-derived mutated mtDNA, promoting cellular senescence and compromising effector functions and memory formation [169]. These findings underscore the previously underappreciated role of mitochondrial dysfunction in driving T cell senescence.

Senescence affects T cells in several ways **(Figure 1C)**. First, regarding surface markers, senescent T cells are typically characterized as $CD28^-CD57^+CD4^+/CD8^+$ T cells [170-172], which is observed in many types of cancer, including lung cancer, ovarian cancer, head and neck cancer, and glioblastoma, as mentioned above [173-176]. Additionally, senescent T cells possess an increased expression of Tim-3, KLRG-1, and re-expression of the naïve T cell marker CD45RA [177, 178]. Expression of PD-1 and CTLA-4 was also observed in patients with acute myeloid leukemia (AML) and visceral adipose tissue of obese mice [179, 180], suggesting potential immunosuppression. Second, the cytotoxicity of senescent $CD8^+$ T cells is reduced, as evidenced by lower levels of perforins and granzyme B [30, 31, 181], which leads to impaired antitumor immunity [181]. In contrast, senescent $CD4^+$ T cells maintain their cytotoxic potential, with unchanged levels of perforins and granzyme B [182]. Third, senescent T cells acquire SASP, which is related to age-associated inflammation [183]. However, its role within the TME remains unclear. Fourth, senescent T cells modulate

monocytes/macrophages through upregulated surface markers Tim-3 and CD40L [177]. This leads to the production of pro-inflammatory cytokines and angiogenic factors, including TNF, IL-1β, IL-6, MMP-9, VEGF-A, and IL-8 [184]. Interestingly, when co-cultured with senescent T cells, monocytes/macrophages exhibit increased CD16 expression, a characteristic of M2 macrophages [130, 131, 184]. It can be hypothesized that senescent T cells promote the polarization of macrophages from M1 subsets to M2 subsets. Fifth, senescent T cells undergo metabolic reprogramming akin to that of senescent somatic cells, characterized by enhanced glycolysis, mitochondrial biogenesis, and upregulated lipid metabolism [185, 186]. Accumulation of lipid droplets in these cells impairs effector functions and diminishes the efficacy of T-cell–based immunotherapies [187], while increased glycolytic flux further amplifies SASP secretion [185]. Overall, the evidence suggests that T cell senescence promotes a shift towards an immunosuppressive TME.

Accurate discrimination between senescent and exhausted T-cell phenotypes is essential, as both states are marked by functional impairment and co-express inhibitory receptors such as PD-1 and CTLA-4 [179, 180]. First, exhausted T cells are induced by constant stimulation of antigen, including chronic infection and cancer [188], wherein naïve T cells exhibit impaired differentiation into effector/memory subsets. Instead, they progress through precursor exhausted to terminally exhausted states [188]. Conversely, senescent T cells derive from effector or memory T cells [189]. Second, senescent T cells are typically regarded as $CD28^{-}CD57^{+}CD4^{+}/CD8^{+}$ T cells. Early T cell exhaustion is identified by expression of PD-1, TCF-1, and low expression of

EOMES, while terminal T cell exhaustion is identified by high expression of PD-1, EOMES, and loss of TCF-1 [188]. On the contrary, senescent T cells exhibit far lower levels of PD-1 and CTLA-4 compared to exhausted T cells [161]. Third, while immune checkpoint blockade (ICB) can rejuvenate exhausted T cells, it has little effect on senescent T cells [177]. This phenomenon can be attributed to the differential expression of inhibitory receptors [161]. Currently, there are no viable approaches to reverse T cell senescence. Moreover, an optimal therapeutic effect from ICB requires the coreceptor CD28, which is absent in senescent T cells [190, 191]. Fourth, senescent T cells display a highly differentiated phenotype marked by the loss of CD27 and CD28 [4], whereas exhausted T cells can be categorized into several subsets based on their differentiation [192]. Thus, T cell senescence appears to be an irreversible endpoint, whereas T cell exhaustion may represent a reversible process.

Clinically, both senescent $CD4^+$ T and $CD8^+$ T cells were associated with poor survival rates and immunotherapy response in cancer patients [193-195], indicating that they may pose a barrier to effective cancer therapies. In metastatic breast cancer, patients undergoing chemotherapy exhibited a correlation between the increased number of senescent $CD28^-CD57^+$ T cells and shorter progression-free survival (PFS) [196]. This correlation may be due to the elevated levels of IL-6 and IL-10 [196], yet the mechanisms by which senescent T cells impact chemotherapy outcomes remain unclear. Regarding ICB, though it has minimal effects on senescent T cells, T cell senescence has been correlated with a lack of ICB benefit in elderly patients with distinct cancers [18, 194]. Furthermore, aged mice experienced more ICB-induced adverse events

compared to young mice, mediated by the IL-21-CXCL13-auto-antibody axis in $CD4^+$ T cells [40], highlighting senescence as a risk factor for ICB. Nonetheless, a multicenter study found that elderly patients with melanoma responded more efficiently to anti-PD-1 therapy [197]. This paradoxical finding warrants further investigation. It may be that senescent tumor cells become more susceptible to T cell immunity following PD-1-PD-L1 interaction blockade [198]. Together, senescent T cells become dysfunctional and contribute to an immunosuppressive TME, with their clinical implications necessitating further investigation.

5.2. Tregs

Regulatory T cells (Tregs), identified as $CD4^+FOXP3^+CD25^{high}$ T cells, play an important role in regulating tumor immunity. Tregs suppress tumor immunity through five primary mechanisms [199]. In addition, Tregs are capable of inducing immunosenescence [200, 201]. Firstly, Tregs induce DNA damage in T cells via glucose competition, subsequently leading to T cell senescence via p38, ERK1/2, and STAT pathways [200, 201]. Furthermore, a subset of Tregs, known as γδ regulatory T cells, can induce senescence of T cells and DCs in breast cancer models [202]. Interestingly, similar to tumor cells, activation of TLR8 with TLR8 ligands has been found to inhibit Treg-induced senescence by abrogation of Treg activity [201]. Tregs are also influenced by aging. Studies have demonstrated that aged mice exhibit increased numbers of Tregs and higher FOXP3 expression. This subset of Tregs produces elevated levels of IL-10 and suppresses T cells and DCs more effectively compared to their younger counterparts [203]. Single-cell analysis similarly revealed that, in cancers exhibiting a

559 high senescence signature, there was increased infiltration of regulatory T cells (Tregs),
560 which facilitated immune evasion and consequently promoted tumor progression [96].
561 Together, aged Tregs in the TME exhibit enhanced immunosuppressive capabilities.

562 ***5.3. B cells***

563 Historically, B cells were considered minor contributors to tumor immunity, but
564 recent studies have challenged this view [204]. It is now clear that B cells contribute to
565 antitumor immunity through multiple mechanisms. First, activated B cells differentiate
566 into plasma cells that secrete antibodies. IgGs have been found to coat tumor cells,
567 facilitating their internalization by DCs and subsequent T cell activation [205].
568 Moreover, IgG-secreting B cells can inhibit cancer cell growth in early-stage NSCLC
569 [206]. Different from IgGs, IgAs eliminate tumor cells in ovarian cancers through
570 transcytosis [207]. Antibodies also indirectly enhance antitumor immunity through
571 mechanisms including ADCC, antibody-dependent cellular phagocytosis (ADCP), and
572 complement-dependent cytotoxicity (CDC) [204]. Second, B cells have been observed
573 presenting antigens to $CD4^+$ T cells by MHC-II or cross-presenting antigens to $CD8^+$ T
574 cells by MHC-I, thereby activating T cells [204]. Third, recent studies have
575 demonstrated an association between B cells and tertiary lymphoid structures (TLSs)
576 [208]. TLSs are ectopic lymphoid organs beyond classical lymphoid organs, which
577 develop at sites with chronic inflammation [209]. The formation of TLSs relies on
578 interactions between lymphoid tissue inducer cells (LTi cells) and stromal cells
579 mediated by IL-7 and CXCL13 [209]. Subsequently, the production of VEGF,
580 chemokines, and adhesion molecules facilitates the formation of high endothelial

venules (HEVs) and the recruitment of lymphocytes [209]. In injured kidney models, TLS formation was observed in aged but not young mice [210]. Moreover, in aged tumor-bearing mice, IL-21 produced by $CD4^+$ T cells induced CXCL13 secretion, thereby promoting TLS formation [40]. This suggests that aging may drive the formation of TLSs. Mature TLSs create an environment that allows B cells to exert antitumor immunity, while B cells act as 'administrators' of these structures [204, 208]. Interestingly, though TLSs are generally associated with a favorable prognosis in some cancers [204], in aged mice, TLSs promoted by $CD4^+$ T cells led to ICB resistance [40]. Currently, there is insufficient evidence to fully understand the impact of senescent TLSs on tumor development, highlighting the need for further research.

Aging influences B cells in several ways. Specifically, gut microbiota has been shown to induce B cell senescence [211]. With aging, there is a significant decrease in B cells among peripheral blood mononuclear cells (PBMCs) due to reduced B lymphopoiesis in the bone marrow [212]. Despite the decreased number of B cells, an age-related increase in IgG and IgA levels was observed in elderly groups, along with a decrease in IgD and IgM levels [213]. Interestingly, these changes vary between genders [213]. Moreover, inflammaging in aged groups leads to a reduction in B cell progenitors and an accumulation of oncogenic mutations [214]. Although research focuses on the senescence of B cells, the link between senescent B cells and tumor immunity remains to be explored.

6. Stromal senescence: The supportive structure of the TME

We have sequentially introduced the senescence of immune cells, but it is far from

illuminating the complexities of the entire tumor microenvironment. The stroma is important in providing support and structure, promoting angiogenesis, regulating immunity, facilitating metastasis, and conferring chemoresistance during tumor progression, especially in cancers such as pancreatic cancer. It primarily comprises fibroblasts, endothelial cells, pericytes, and adipocytes, together with the extracellular matrix (ECM). Our discussion will focus primarily on the first two types of senescent stromal cells—fibroblasts and endothelial cells—and their roles within the TME.

6.1. Fibroblasts

Fibroblasts play a primary role in stromal formation, with cancer-associated fibroblasts (CAFs) receiving significant attention for their role in tumor progression. CAFs segregate into inflammatory CAFs (iCAFs) and myogenic CAFs (myCAFs), differentiated by their spatial localization [215]. iCAFs are located away from tumor cells, whereas myCAFs are adjuvant to tumor sites [215]. By secreting cytokines, chemokines, and other effector molecules, CAFs directly or indirectly remodel the TME, which involves crosstalk with immune cells, including polarization of immune cells, regulation of immunity, reduction of cytotoxic cytokines, upregulation of inhibitory receptors, and remodeling of the extracellular matrix (ECM) [216].

Various factors can induce fibroblast senescence. Radiotherapy causes DNA damage in fibroblasts, thereby triggering DDR and inducing senescence [217]. Novel therapies, such as CDK4/6 inhibitors, induced senescence of fibroblasts through the downregulation of Mdm2 in a melanoma model [15]. Histone deacetylase (HDAC) inhibitors, used to treat various tumors including T cell lymphoma and multiple

myeloma, induce fibroblast senescence without DNA damage [218]. Interestingly, obesity increases the levels of deoxycholic acid in the enterohepatic circulation, which in turn drives the senescence of hepatic stellate cells through DDR [219], highlighting obesity as a significant contributor to stromal senescence.

The tumor-promoting nature of senescent fibroblasts was first suggested by A. Krtolica *et al.* in 2001, demonstrating their role in tumorigenesis in aged organisms [29]. Subsequent research has reinforced this finding. During tumor initiation, senescent fibroblasts promoted ovarian tumorigenesis, as evidenced by reduced tumor growth following the abrogation of the senescence program [220]. Further studies indicate that IL-4 or IL-10-mediated Th2 immunity, which is activated by NF-κB, predisposes aged H-Ras-activated mice to squamous cell carcinoma compared to younger counterparts [221]. MMP-3, secreted by senescent fibroblasts, leads to the dedifferentiation of premalignant epithelial cells, thereby increasing tumorigenesis risk [222]. Moreover, stroma-derived osteopontin (OPN), a component of the ECM, facilitated premalignant cell growth in elderly groups [223]. Interestingly, beyond endocrine effects, senescent fibroblast also stimulates neoplastic epithelial cell proliferation through the production of amphiregulin (AREG) in prostate models [224]. Together, stromal senescence robustly induces tumorigenesis through multiple mechanisms.

Although senescent fibroblasts are often tumor-promoting, some studies indicate that during early stages, stromal senescence aids in recruiting immune cells **(Figure 2A)**, thereby facilitating the clearance of senescent cells and reducing cancer risk. In fibrotic murine livers, senescent HSCs exhibited increased ECM degradation, coupled with

enhanced immune surveillance mediated by NK cells [225]. In another murine liver fibrosis model, p53-induced senescence of HSCs resulted in macrophage polarization towards M1 subsets, mediated by SASP, including IL6 and IFN-γ [22]. M1 macrophages, in turn, eliminate senescent HSCs, thereby limiting tumorigenesis [22]. Though evidence has shown that senescent tumor cells can induce immune surveillance in several models, in addition to livers such as multiple myeloma and lung cancers [8], data on similar properties in senescent fibroblasts outside the liver are limited and warrant further investigation.

During advanced stages of tumors, senescent fibroblasts are pivotal in tumor invasion, metastasis, angiogenesis, and a poor prognosis **(Figure 2B)**. First, senescent fibroblast-derived MMP-2 and TGF-β induced keratinocyte invasion in squamous cell carcinoma models [226]. Second, excessive IL-8 secreted by senescent fibroblasts enhanced invasion and metastasis in pancreatic cancer [227]. The levels of IL-8 and stromal senescence, as represented by expression of $p16^{INK4a}$, were associated with a poor prognosis of patients with pancreatic cancer [227]. In another research, IL-6 and IL-8 induced EMT and stemness of breast cancer cells, as demonstrated by fibroblastoid morphology, increased expression of CD44, and enhanced self-renewal capabilities in tumor cells, making them more aggressive [228]. Third, regarding angiogenesis, while

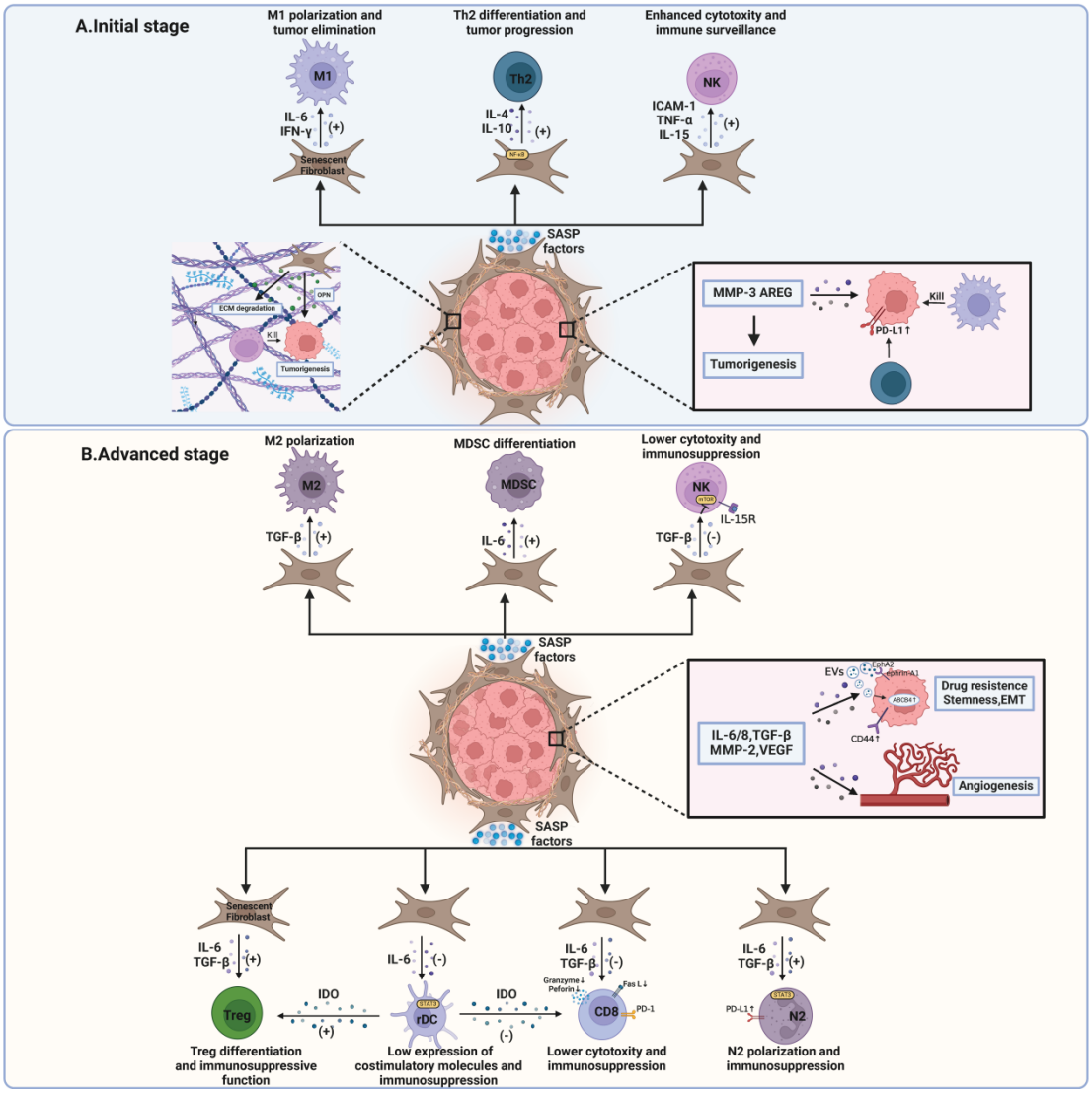

Fig.2 **Impacts of SASP produced by senescent fibroblasts within the tumor microenvironment. A** At the initial stage, senescent fibroblasts release SASP factors that encourage antitumoral immune responses. M1 macrophage polarization and NK cell-mediated cytotoxicity are bolstered by these factors. Additionally, ECM degradation by SASP factors facilitates enhanced immunosurveillance by NK cells. Conversely, other SASP factors may promote tumorigenesis through interactions with Th2 cells, which upregulate the expression of PD-L1 on tumor cells. ECM components like OPN can aid in tumor growth. **B** At advanced stages, SASP factors play a pivotal role in tumor progression. On one hand, they can induce cancer stemness, promote epithelial-mesenchymal transition (EMT), confer chemotherapy resistance, and stimulate angiogenesis. On the other hand, SASP factors from senescent fibroblasts contribute to an immunosuppressive microenvironment. This includes the recruitment of MDSCs, M2 and N2 polarization, inhibition of NK cell cytotoxicity, and Treg cell enhancement, which collectively inhibit effective anti-tumor immune responses. The interactions between PD-1 on T cells and PD-L1 on tumor cells further facilitate immune evasion by the tumor. MMP, matrix metalloproteinase; OPN, osteopontin; ECM, extracellular matrix; AREG, amphiregulin; ICAM-1, intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-α; IL, interleukin;

IFN-γ, interferon-γ; TGF-β, transforming growth factor-β; EVs, extracellular vesicles; VEGF, vascular endothelial growth factor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; EMT, epithelial-mesenchymal transition; NK, natural killer; Th2, helper T cell 2; rDC, regulatory dendritic cell; IDO, indoleamine 2,3-dioxygenase; ABCB4, ATP-binding cassette subfamily B member 4; EphA2, erythropoietin-producing hepatocellular A2; ephrin-A1, recombinant human Ephrin A receptor 1. This figure was created with BioRender (https://biorender.com/).

early studies suggested reduced vascularization in aged tumor-bearing mice [229], subsequent research supports the idea that stromal senescence promotes vascularization via increased production of VEGF and TGF-β [27, 28]. Fourth, extracellular vesicles (EVs), as heterogeneous types of membrane vesicles important for intracellular communication, were secreted by senescent fibroblasts [230, 231]. Exosome, as a special category of EVs, was also found to be released in prostate cancers [232]. Not only did EVs promote tumor proliferation through EphA2-ephrin-A1 interaction [231], but they also resulted in drug resistance via inducing expression of ATP-binding cassette subfamily B member 4 (ABCB4) [230]. Interestingly, although traditional approaches emphasize inhibiting tumor angiogenesis [233], senescence-induced angiogenesis could be therapeutically employed [89, 90]. Induced by MEK and CDK4/6 inhibitors trametinib and palbociclib (T/P), senescence successfully triggers SASP, including a series of pro-angiogenesis factors, which surprisingly enhances the therapeutic effect of chemotherapy and ICB in KRAS mutant pancreatic ductal adenocarcinoma (PDAC) [89, 90]. This approach capitalizes on the desmoplastic nature of PDAC, which impedes drug delivery to tumor sites [234, 235]. However, the viability of promoting angiogenesis through senescence in other tumor types remains uncertain. Finally, senescent fibroblasts upregulated gene expression relating to

710 immune regulation and SASP, resulting in impaired $CD8^+$ T cell cytotoxicity and poor
711 responsiveness to immunotherapy and chemotherapy [236-239]. The presence of
712 senescent fibroblasts is correlated with a poor survival outcome using machine learning
713 [238, 239].

714 ***6.2. Endothelial cells***

715 It is important to note that the stroma consists of more than just fibroblasts. Tumor-
716 associated endothelial cells (ECs) also significantly impact the TME as a crucial
717 stromal component. Analysis across various cancer types reveals that ECs exhibit the
718 highest rate of cellular senescence among all cell types in the vascular compartment of
719 cancers [240]. In liver sinusoids, the majority of $p16^{INK4a}$-expressing senescent cells are
720 ECs [241]. Indeed, ECs are particularly susceptible to senescence, being the first cell
721 types affected by metabolites and senescence stimuli [46]. Due to their critical location,
722 various factors contribute to the senescence of ECs. Metabolites and hormones,
723 including insulin, glucose, triglycerides, cholesterol, amino acids, ROS, endothelin I,
724 and angiotensin II, can induce EC senescence. Senescent ECs, in turn, produce higher
725 levels of ROS, endothelin I, and angiotensin II, creating a vicious cycle [46].
726 Specifically, nitric oxide, crucial for vasodilation, is believed to attenuate EC
727 senescence [47, 242]. Conversely, the endothelial nitric oxide synthase (eNOS) is
728 impaired in senescent ECs [243], indicating the interplay between NO and senescence.
729 Cytokines such as TNF-α and TGF-β can induce senescence of ECs [47, 244].
730 Moreover, like other cells, conventional cancer therapies [47, 245-247], targeted
731 therapies including receptor tyrosine kinase inhibitors, VEGF inhibitors, and CDK4/6

732 inhibitors can all induce senescence of ECs [47, 248, 249]. Interestingly, kisspeptin-10
733 (KP-10), a member of multifunctional peptides inhibiting metastasis of cancers, can
734 induce endothelial senescence [250]. In melanoma models, ECs exhibit upregulation of
735 Krüppel-like factor 4 (KLF4), which induces senescence of ECs [13]. This suggests
736 indirect tumor cell involvement in EC senescence.

737 Senescent ECs have a dual role in tumor development **(Figure 3)**. On one hand,
738 senescent ECs induce self-elimination by immune surveillance to evade tumorigenesis
739 [21], with impaired angiogenesis capacity demonstrated by reduced proliferation and
740 VEGF levels [247, 251]. The benefit of this for cancer patients remains to be determined.
741 On the other hand, senescent ECs promote tumor metastasis and treatment resistance
742 via secretion of SASP [12, 13, 246]. Moreover, the sustained activity of Notch1
743 receptors is observed in senescent ECs, which further promotes cancer metastasis
744 through the production of VCAM-1 [249, 252]. Interestingly, though impaired
745 angiogenesis was observed in senescent ECs, tumor-derived EVs can inhibit the
746 senescence of ECs, thereby counteracting such effects [253]. Moreover, senescent EC-
747 derived EVs can promote the proliferation and migration of tumor cells [253]. The pro-
748 inflammatory profile of senescent ECs offers potential for survival prognostication and
749 immunotherapy efficacy prediction using machine learning [240, 254], promising
750 avenues for targeting or using senescent ECs as biomarkers.

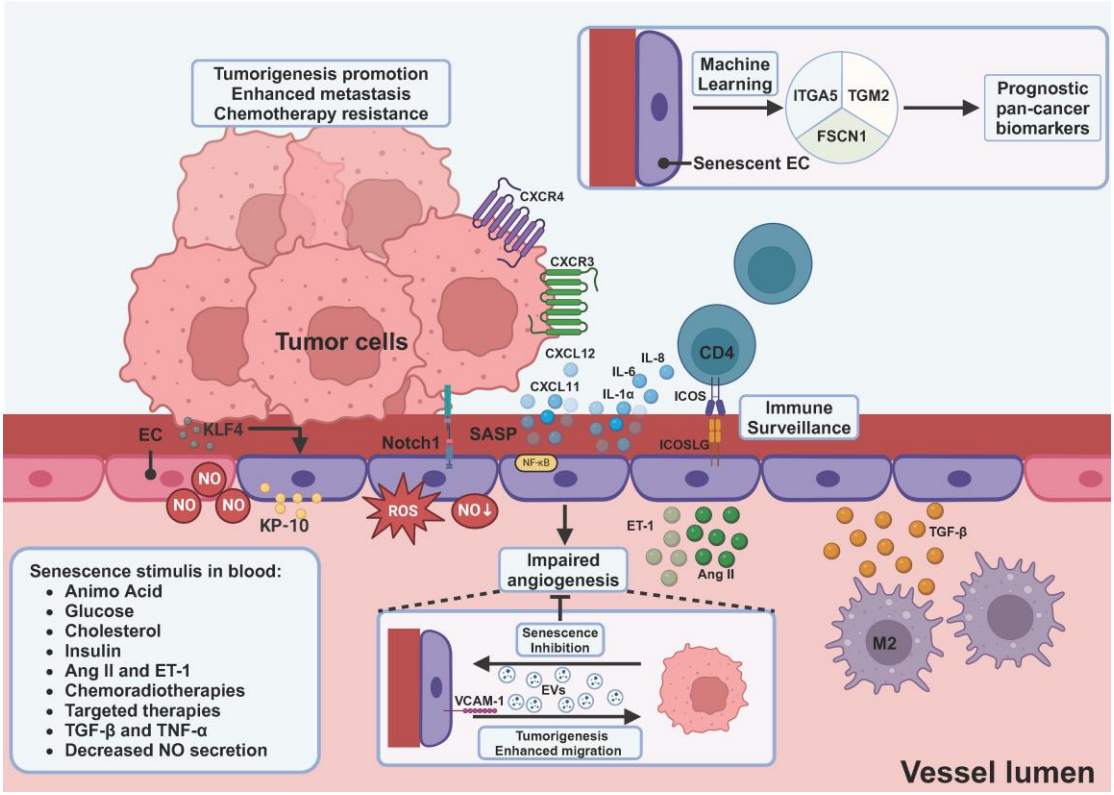

Fig.3 **Induction and impact of endothelial cell senescence within the tumor microenvironment.** Endothelial cells, as another important component of stroma, specifically become senescent when they encounter metabolites and hormones, including glucose, cholesterol, insulin, etc. M2-derived TGF-β can be another source of induction. Senescent endothelial cells produce increased levels of angiotensin II, endothelin 1, ROS, and decreased levels of NO, which in turn induce senescence of endothelial cells. Tumor-secreting KP-10 and upregulation of KLF4 on ECs can induce senescence of ECs. SASP factors produced by senescent endothelial cells have dual effects. On one hand, they lead to self-immunosurveillance mediated by $CD4^+$ T cells. On the other hand, CXCL12 and CXCL11 can promote tumor cell metastasis and resistance to chemotherapy. Tumor-derived EVs are able to inhibit senescence of ECs, thereby counteracting the impaired angiogenesis of senescent ECs. Moreover, senescent EC-derived EVs and upregulation of VCAM-1 can promote proliferation, and migration of tumor cells. Using machine learning, ITGA5, TGM2, and FSCN1 were screened to be the potential prognostic pan-cancer biomarkers. EC, endothelial cell; NO, nitro oxide; Ang II, angiotensin II; ET-1, endothelin 1; KLF4, Kruppel-like factor 4; KP-10, kisspeptin-10; CXCL, C-X-C motif ligand; CXCR, C-X-C motif receptor; ICOS, inducible T cell co-stimulator; ICOSLG, inducible T cell co-stimulator ligand; VCAM-1, vascular cell adhesion molecule-1; ITGA5, integrin subunit alpha 5; TGM2, transglutaminase 2; FSCN1, fascin actin-bundling protein 1. This figure was created with BioRender (https://biorender.com/).

7. Role of SASP within the TME: A double-edged sword

In the previous section, we have detailed the senescent immune and stromal cells within the TME. Notably, SASP is increasingly recognized as a key mediator of cellular senescence. Earlier perspectives suggested that senescent cells acquire SASP only when cellular senescence is triggered by DNA damage or the DNA damage response (DDR) [54, 255]. However, current research suggests that SASP induction is a complex process mediated by multiple pathways [8, 41]. Four primary pathways are now identified as mediators of SASP induction: p53-p21/p16-Rb, DDR-NF-κB, p38 MAPK, as well as mTOR and cytoplasmic DNA-cGAS-STING pathways [8, 256]. Additionally, SASP is regulated by epigenetic mechanisms and oxylipins, such as dihomo-15d-PGJ2 [256]. The heterogeneity of SASP is influenced by the cell type and the causes of senescence, with IL-6 and IL-8 being commonly identified SASP factors [8]. In this section, we will concentrate on the dual role of SASP in tumor progression. Research indicates that SASP secretion is influenced by tissue type, cell type, and stage of progression. Specifically, SASP dynamics within the tumor microenvironment can be categorized into two distinct stages.

During tumor initiation, SASP factors help eliminate potential pre-malignant cells. Senescent hepatocytes contribute to tumor surveillance through SASP-mediated senescence surveillance [80, 257], which relies on the participation of immune cells. These two studies underscore the importance of timely senescence surveillance in the liver. This has also been demonstrated in other cancers, including lymphoma, melanoma, and osteosarcoma, where innate immunity-mediated clearance of senescent cells provides tumor-suppressive effects [8, 45]. Specifically, senescent pre-malignant

796 cells may give rise to cancer if not cleared promptly. Senescent fibroblasts within the
797 TME, as previously described, also exhibit anti-tumor activity during the early stages
798 of tumor development. An exception arises in KRAS-driven lung cancer, where
799 senescent macrophage SASP unexpectedly promotes early tumorigenesis [23],
800 underscoring the need for deeper investigation into immune-derived SASP.

801 In established tumors, SASP fosters invasion, metastasis, and neovascularization,
802 which we have elaborated on in the section on senescent fibroblasts. Senescent ECs
803 produce SASP factors fostering metastasis in breast cancer [12] and melanoma models
804 [13] and contributing to chemotherapy resistance [246]. Moreover, the
805 immunosuppressive microenvironment created by SASP factors should be emphasized.
806 IL-6 regulates both innate and adaptive immunity. In innate immunity, through IL-6-
807 STAT3 signaling, HCC-derived CAFs activate and maintain PD-L1^{+} neutrophils, thus
808 impairing T cell function via PD-1-PD-L1 interaction [258]. What's more, HCC-
809 derived CAFs secreted IL-6 to generate regulatory DCs, which contribute to the
810 dysfunction of T cells and the promotion of Treg activity via indoleamine 2,3-
811 dioxygenase (IDO) upregulation [259]. CAF-derived IL-6 promotes the differentiation
812 of monocytes into myeloid-derived suppressor cells (MDSCs), thereby mediating
813 immune dysfunction, which has been observed in HCC [260], pancreatic cancer [261],
814 and esophageal squamous cell carcinoma [262]. The extracellular matrix secreted by
815 senescent fibroblasts was also able to limit NK cell cytotoxicity [263]. In adaptive
816 immunity, CAFs can directly enhance Treg function while inhibiting T cell proliferation
817 through IL-6 production [264]. Meanwhile, TGF-β, as another component of SASP [54],

818 also acts as a regulator in tumor immunity. TGF-β not only promotes the transformation
819 of monocytes into M2 macrophages [216] but also induces N2 neutrophil polarization
820 in HCC [265]. Moreover, TGF-β blocks IL-15-induced activation of mTOR, which is
821 essential for cytotoxicity and proliferation of NK cells [266]. Suppression of TGF-β
822 successfully abrogated metastases in two mouse models [266]. TGF-β derived from
823 CAFs also promotes both Th17 differentiation and the conversion of $CD4^+$ naïve T cells
824 into Tregs [267, 268] while inhibiting the production of perforin, granzyme B, FasL,
825 and IFN-γ by $CD8^+$ T cells [269]. Collectively, SASP factors produced by senescent
826 cells are broadly immunosuppressive in advanced stages of tumors.

827 **8. Novel therapies targeting senescence: Next hope for cancer treatment?**

828 The advent of novel immunotherapies, including ICB, engineered chimeric
829 antigen receptor (CAR) T cells, and cancer vaccines, has ushered in a new era in cancer
830 treatment. Despite its success, ICB faces resistance driven by genetic and epigenetic
831 aberrations in tumor cells, T cell exhaustion, cancer-associated fibroblasts (CAFs), and
832 immunosuppressive mechanisms [270]. Consequently, there is an urgent need to
833 overcome these obstacles. Emerging evidence highlights the promising potential of
834 targeting senescence to enhance the efficacy of ICB. These approaches fall into four
835 categories—induction of senescence, regulation of SASP, clearance of senescence, and
836 senescence reprogramming **(Figure 4)**.

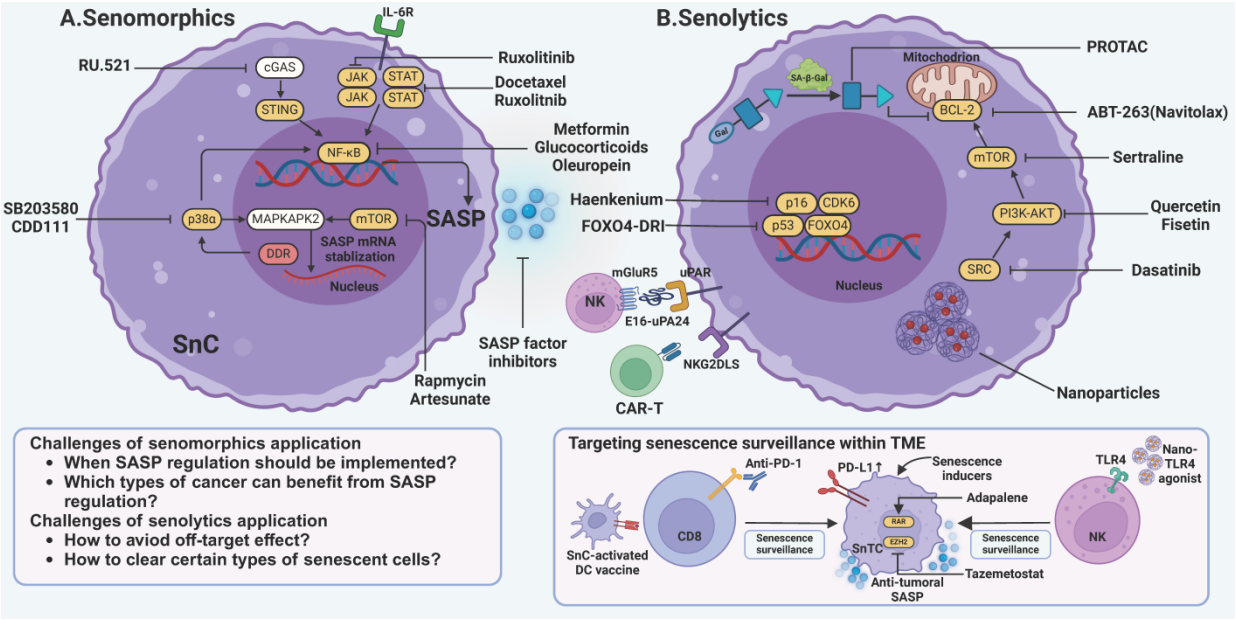

Fig.4 **Targeting senescence by modulation of SASP or clearance of senescent cells.** **A** One strategy to target senescence involves preventing senescent cells from producing tumor-promoting SASP factors. These drugs, termed senomorphics, primarily act on pathways such as cGAS-STING, JAK-STAT, and p38α-MAPKAPK2. Key mechanisms include NF-κB and mTOR to inhibit SASP production. Drugs such as metformin and rapamycin are among those used to modulate these pathways and mitigate the detrimental effects of SASP. **B** Another widely used strategy is to eliminate senescent cells with senolytics. The first-generation senolytics target anti-apoptotic pathways intrinsic to senescent cells, such as those involving BCL-2, PI3K-AKT, and mTOR. Second-generation senolytics find a new path by targeting specific surface markers on senescent cells. It utilizes innovative techniques like CAR-T cells, chimeric polypeptides, and vaccines. Notably, efforts are being made to enhance senescence surveillance mediated by T cells and NK cells. JAK, janus kinase; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor-κB; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; STING, stimulator of interferon genes; mTOR, mammalian target of rapamycin; MAPKAPK2, mitogen-activated protein kinase-activated protein kinase 2; DDR, DNA damage response; BCL-2, B-cell lymphoma-2; PI3K, phosphatidylinositide 3-kinases; CAR-T, chimeric antigen receptor-T; GPNMB, glycoprotein nonmetastatic melanoma protein B; uPAR, urokinase-type plasminogen activator receptor; NKG2DLS, Natural killer group 2 member D ligands; SnC, senescent cell; SnTC, senescent tumor cell. This figure was created with BioRender (https://biorender.com/).

8.1. Induction of senescence

In the early stages of tumors, senescence exerts antitumoral effects through several mechanisms, including clearance of senescent cells, activation of tumor immunity, and

promotion of proper angiogenesis, as discussed above [89, 90, 225, 270]. Indeed, inducing senescence can improve the effect of cancer treatment **(Figure 4)**. T/P-induced senescence fosters the accumulation of $CD8^+$ T cells, leading to increased sensitivity to ICB and chemotherapy in human PDAC models [89, 90]. Interestingly, the desmoplastic nature of PDAC, which is typically resistant to drug treatment, was shown to benefit from T/P-induced SASP factor production, which promoted vascularization and improved drug delivery and chemotherapy response [89, 90]. Additionally, induction of senescence stimulated the production of antitumoral SASP factors, leading to NK cell-mediated tumor clearance [271]. EZH2 is a key gene regulating SASP secretion, whose blockade combined with ICB has successfully promoted the production of SASP chemokines, including CCL2 and CXCL9/10, leading to T cells and NK cells-mediated tumor immunity [11]. Nanoparticles co-delivering senescence inducers and TLR4 agonists extend survival in PDAC by activating T cells and NK cells [272]. Ali and JAK2 inhibitor ruxolitinib could also recruit T cells and NK cells within TME by inducing SASP secretion [273]. DC vaccines loaded with senescent tumor antigens or PD-1 blockade further potentiate T cell responses [198, 274]. Conclusively, T cells and NK cells are emerging as the primary force in eliminating senescent cells with the support of SASP. Beyond preclinical studies, clinical trials have explored inducing senescence with dexamethasone to re-sensitize response to ICB in patients with NSCLC (NCT04037462).

To harness the antitumor benefits of TIS while mitigating its deleterious immunosuppressive effects, two principles may guide clinical implementation. First,

886 the temporal window for senolytic intervention is critical. Extended persistence of
887 senescent cells within the TME fosters immunosuppression, angiogenesis, and
888 metastatic niche formation as discussed above. Thus, senolytics should be deployed
889 once TIS has maximally engaged immune-mediated tumor clearance but prior to the
890 onset of a full-blown SASP or escape from growth arrest by senescent cells [275].
891 Second, current senescence-inducing modalities—chemotherapy, radiotherapy, and
892 kinase inhibitors—lack specificity and can inadvertently drive senescence in immune
893 effector populations, exacerbating immune dysfunctions [14, 19]. To obviate this,
894 agents that selectively target tumor-cell senescence are required. For example,
895 pharmacological inhibition of the replication origin kinase CDC7 induces senescence
896 specifically in hepatocellular carcinoma cells without impairing normal immune cells
897 [276]. Similarly, the natural alkaloid tryptanthrin (TRYP) rapidly triggers senescence
898 in liver cancer cells, arresting proliferation while sparing systemic immunity [277].

899 ***8.2. Regulation of SASP***

900 Conversely, inhibiting the tumor-promoting SASP factors also emerges as a plausible
901 alternative. **(Figure 4A)**. Drugs targeting SASP pathways are referred to as
902 senomorphics. Key intervention points include transcriptional regulators, signal
903 transduction cascades, metabolic nodes, and the SASP factors themselves [8, 41, 48].
904 For instance, inhibiting the JAK2/STAT3 pathway, which is involved in SASP-
905 associated tumor growth and chemoresistance, induces robust immune surveillance in
906 $Pten^{null}$ tumors with docetaxel-induced senescence [278]. Targeting PTBP1 via RNA
907 interference prevented the protumoral effects of SASP factors in tumor-bearing mice

[279]. NF-κB and mTOR have emerged as prominent targets for mitigating senescence [8, 92, 93]. Metabolic reprogramming in senescent cells further dictates SASP output: in pancreatic cancer models, elevated NAD^+ flux enhances NF-κB–dependent proinflammatory SASP [280], whereas inhibition of nicotinamide phosphoribosyltransferase (NAMPT)—the rate-limiting enzyme of the NAD^+ salvage pathway—dampens SASP release and suppresses tumor growth [280]. In the hepatic niche, loss of the gluconeogenic enzyme fructose-1,6-bisphosphatase 1 (FBP1) in hepatocytes triggers secondary senescence of hepatic stellate cells via HMGB1 signaling; neutralization of extracellular HMGB1 attenuates HSC-derived SASP and impairs tumor progression [281]. Interestingly, metformin, a common medication for type II diabetes, can suppress NF-κB pathways [282]. It can also inhibit T cell senescence while maintaining its cytotoxicity [283]. Though metformin has shown potential in attenuating aging [284], NF-κB suppression unfortunately led to drug resistance and a poor prognosis in murine lymphoma and melanoma models [92, 93]. Epidemiological studies suggest a decreased incidence of cancer in individuals receiving metformin [285], suggesting its potential role in cancer prevention rather than treatment.

The mTOR-MK2 pathway also plays a crucial role in SASP production [286-289]. mTOR inhibitors like rapamycin reduce the secretion of tumor-promoting SASP factors [288, 289]. In a phase IIa randomized controlled trial, the use of rapamycin enhanced the response to influenza vaccination [290], demonstrating its potential to boost immunity. Moreover, unlike other mTOR inhibitors, brief administration of rapamycin

can produce a sustained anti-SASP effect, thereby reducing the risk of adverse events associated with long-term treatment [291]. To date, clinical studies evaluating rapamycin's efficacy in targeting senescence remain in the early stages **(Table 2)** [292].

Table 2: Current clinical trials targeting senescence against cancers

Category	Drug	Mechanism	Combination therapy	Condition	Design	Reference	Status
Regulation of senescence	Dexamethasone	Induction of senescence	Anti-PD-1 therapy	NSCLC	Phase I/II	NCT04037462	Terminated
	Rapamycin	Inhibition of SASP	Alisertib	Advanced Solid Tumors	Phase I	[292]	With result
Clearance of senescence	D plus Q	1st-generation senolytics	None	Childhood Cancer	Phase II	NCT04733534	Recruiting
			Anti-PD-1 therapy	Head and Neck Cancer	Phase II	NCT05724329	Active
			None	Triple-negative Breast Cancer	Phase II	NCT06355037	Recruiting
	Fisetin	1st-generation senolytics	None	Childhood Cancer	Phase II	NCT04733534	Recruiting
			None	Breast Cancer	Phase II	NCT05595499	Recruiting

			None	Breast Cancer	Phase II	NCT06113016	Recruiting
	ABT-263 (Navitoclax)	1st-generation senolytics	Gemcitabine	Advanced solid tumors	Phase I	[293]	With result
			Docetaxel	Advanced solid tumors	Phase I	[294]	With result
			None	Lymphoid malignancies	Phase IIa	[295]	With result
			Rituximab	Chronic lymphocytic leukemia	Phase II	[296]	With result
	ABT-737	1st-generation senolytics	None	Ovarian Cancer	Observational study	NCT01440504	Completed
	"One-two" punch therapy	Induction of senescence plus senolytics	Decitabine plus navitoclax	Acute myeloid leukemia	Phase Ib	NCT05222984	Active
			Olaparib plus navitoclax	Triple-negative Breast Cancer	Phase I	NCT05358639	Active

NSCLC, non-small-cell lung cancer; D, dasatinib; Q, quercetin; SCLC, small-cell lung cancer.

933

These findings raise the question: Can the regulation of SASP factors signify the next breakthrough in cancer therapy? The dual role of SASP in tumor development complicates its clinical application. Thus, balancing the antitumoral and protumoral effects of SASP factors is crucial. Based on current research on SASP so far, several key characteristics of SASP can be identified. The secretion of SASP factors is stage-dependent and tissue-dependent, which presents two major challenges. First, determining when SASP should be induced or inhibited remains a critical question. At present, it remains challenging to determine whether SASP is beneficial or detrimental for a particular patient. Nor can the exact point at which the role of SASP is reversed be identified. However, since many cancers are diagnosed at advanced stages, it may be more beneficial to inhibit the production of SASP factors to achieve improved clinical outcomes. Second, for certain tumor types, it remains unclear which strategy is optimal. The answer may lie in identifying which component of the SASP factors is dominant in regulating the TME as a whole. For instance, in pancreatic ductal adenocarcinoma (PDAC) models, pro-angiogenic factors produced by senescent cells can promote the formation of a more 'open' microenvironment, thereby enhancing the response to chemotherapy and immunotherapy [89, 90]. While in lymphoma models. In lymphoma models, IL-6 produced by senescent endothelial cells (ECs) has been shown to protect tumor cells from chemotherapy [246]. Overall, the future of regulating SASP as an effective cancer therapy is likely to be personalized.

8.3. Clearance of senescence

Senescent cell clearance via senolytics, drugs that selectively ablate senescent cells,

956 is a second therapeutic strategy **(Figure 4B)**. Unlike SASP inhibitors, senolytics
957 remove the SASP source and can be dosed intermittently [297]. Currently, there are two
958 generations of senolytic drugs. First-generation senolytics target multiple antiapoptotic
959 pathways (SCAPs) in senescent cells, such as BCL-2, SRC kinases, PI3K-AKT, etc. In
960 contrast, targets of second-generation senolytics are discovered via high-throughput
961 library screens, and include lysosome-targeted agents, vaccine-based approaches,
962 nanoparticle delivery, and CAR-T cell strategies [297].

963 Classic first-generation senolytics strategies include dasatinib (D) plus quercetin (Q)
964 and navitoclax (ABT-263). D plus Q induces senescent cell death by inhibiting tyrosine
965 kinase and PI3K signaling, respectively [298]. The combination of D and Q has been
966 observed to alleviate symptoms and increase survival rates in various age-related
967 diseases, including postmenopausal osteoporosis [299], intervertebral disc
968 degeneration [300], diabetic kidney disease [301], and SARS-CoV-2 [302]. D plus Q
969 can indirectly suppress tumor development and metastasis by mitigating stromal
970 senescence [303, 304]. This effect is attributed to the inhibition of protumoral SASP
971 secreted by senescent fibroblasts and stem cells [303, 304]. Clinical trials
972 (NCT04733534, NCT05724329, NCT06355037) are ongoing to determine whether D
973 plus Q can be a viable approach to reverse chemoresistance or to improve survival as
974 an effective and safe adjuvant therapy. ABT-263, one of the BCL-2 inhibitors, has
975 demonstrated greater success in the context of cancer therapy, with the capacity to
976 eliminate therapy-induced senescent cells in cancer models such as lung cancer, breast
977 cancer, melanoma, ovarian cancer, and prostate cancer [45, 298, 305]. In preclinical

978 studies, ABT-263 reversed side effects associated with TIS, including bone marrow
979 suppression, cardiac dysfunction, and cancer recurrence [306]. Clinical studies
980 combining ABT-263 with chemotherapy are in progress **(Table 2)** [45, 293-296, 307].
981 Finally, fisetin is another promising senolytic targeting senescence in cancers. Fisetin
982 is extracted from vegetables and fruits, with a mechanism of action similar to that of
983 quercetin [298, 308]. In patients with small-cell lung cancers, fisetin successfully
984 reversed the chemotherapy resistance induced by cellular senescence [309]. Several
985 phase II clinical trials (NCT04733534, NCT05595499, NCT06113016) are underway
986 to evaluate its efficacy and safety targeting cancers.

987 Despite the promise, senolytics have drawbacks. First, patients receiving ABT-263
988 are at risk of developing thrombocytopenia and neutropenia [45, 297], raising concerns
989 about its safety. Second, resistance to BCL inhibition in senescent tumor cells has been
990 reported [310, 311], though efforts are underway to target mitochondrial apoptotic
991 pathways or employ sensitizer proteins to restore sensitivity to senolysis [310, 312].
992 Third, D plus Q failed to directly kill senescent cells and even exhibited tumor-
993 promoting effects when used alone in animal HCC models due to the poor penetration
994 in tumor sites [313, 314]. The potential of D plus Q in cancer treatment may be realized
995 through novel delivery approaches, such as extracellular vesicles and nanoparticles
996 [314, 315]. Fourth, the elimination of certain senescent cells may cause adverse
997 consequences [241]. For example, acute clearance of senescent ECs in livers will
998 compromise blood-tissue barriers, potentially accelerating liver fibrosis [241]. In light
999 of these limitations, targeting specific markers to clear senescent cells, or eliminating

certain types of senescent cells, has emerged as an alternative approach, namely the second-generation senolytics.

Second-generation senolytics exhibit enhanced target specificity, exploiting senescence-associated pathways through integrated immunotherapeutic strategies—including cancer vaccines, CAR-T cells, and antibody-drug conjugates (ADCs)—to achieve selective clearance **(Figure 4B)** [297]. SA-β-Gal is overexpressed in senescent cells, which is the most commonly used senescence marker [11, 47]. Not only can it be applied to specifically deliver ABT-263 [316], but it can also be recognized by engineered proteolysis-targeting chimeras (PROTACs), thereby selectively eliminating senescent cells [317-321]. Composed of a galactose (Gal) moiety, PROTACs like ARV-771 and MS999 can effectively clear senescent tumor cells without inducing significant adverse events [315, 318]. Another PROTAC drug 753b targeted BCL-xL and BCL-2 dually to inhibit tumor progression [321]. Moreover, new senescence markers are being found. For instance, urokinase-type plasminogen activator receptor (uPAR), a surface protein broadly expressed in T/P induced senescent cells, can be targeted by CAR-T cells, and its elimination improved the prognosis of mice with lung adenocarcinoma [87, 88, 322]. Moreover, using a chimeric polypeptide, uPAR-expressing senescent cells can be cleared by NK cells [323]. Natural killer group 2 member D ligands (NKG2DLs), another surface marker widely expressed in senescent cells, can be targeted by CAR-T cells safely [324]. The effectiveness of this approach in cancer treatment requires further investigation. Notably, CAR-T cells, like conventional T cells, may also undergo senescence [48]. First, children and young adults with B-ALL have

benefited most from CAR-T therapy [325], and current clinical trials have yet to report great benefits in elderly patients (NCT05523661, NCT04537442, NCT05707273, NCT04300998). Second, research has observed increased expression of CD57 on CAR-T cells in the highly malignant glioblastoma multiforme models [326], and modulating p53 signaling pathways helps enhance CAR-T therapy in patients with chronic lymphocytic leukemia [327], suggesting the potential for CAR-T cell senescence. Finally, targeting metabolic dependencies of senescent tumor cells offers an additional avenue for senolytic intervention, given their heightened reliance on glycolysis and glutaminolysis for survival [55, 56]. Indeed, inhibiting glucose uptake or metabolism induces apoptosis selectively in senescent tumor cells [328], while blockade of glutamine utilization suppresses their escape from growth arrest [100]. A potential of mitochondrial-targeted therapy is also suggested. Mitochondrial physiology likewise serves both as a vulnerability and a biomarker for senolytic sensitivity [329-331]. Specifically, pharmacologic inhibition of the TBK1–ATAD3A–Pink1 axis attenuates Pink1-mediated mitophagy, mitigates cellular senescence, and enhances chemotherapeutic efficacy [329]. Moreover, mitochondrial dependence on BCL-XL and MCL-1 has emerged as a robust biomarker for forecasting senescent cell responsiveness to ABT-263 [330, 331]. Collectively, these findings position mitochondrial targeting at the forefront of next-generation anti-senescence therapies.

Based on the success of immunotherapy in cancer treatment, there is growing interest in targeting senescence to reverse the immunosuppressive microenvironment, thereby resensitizing immunotherapy. Senescent tumor cell clearance has been proven

to reverse the immunotherapy resistance associated with the accumulation of senescent cells [19]. Senolytics disrupted SASP-mediated PD-L1/TGF-β signaling axis and replenished intratumoral $CD8^+$ T cells with restored granzyme B expression by normalizing TME arginine metabolism via arginase-1 suppression [19]. Neutralization of senescent-cell–derived mtDNA reverses PMN-MDSC–mediated immunosuppression, enhances T-cell function, and potentiates chemotherapy [102, 169, 332]. Beyond malignant cells, senescent immune and stromal populations are also amenable to targeting **(Table 3)**. Inhibition of cholesterol biosynthesis and lipid droplet formation prevents T-cell senescence and restores checkpoint-inhibitor efficacy [168, 187]. CD153, highly expressed in senescent T cells, can be recognized and eliminated by the CD153-CpG vaccine in mice with obesity-induced senescence [333]. One year after the first vaccine was invented, another seno-antigen glycoprotein nonmetastatic melanoma protein B (GPNMB) was screened via analysis of the transcriptome, and vaccination against GPNMB on senescent ECs was also effective in clearing senescent cells in mice with obesity-induced senescence [334]. Moreover, the elimination of senescent fibroblasts with senolytics awakened T cells and NK cells-mediated tumor immunity and resensitized response to chemotherapy in breast cancers and pancreatic cancers [236, 237, 263]. Senescent macrophages can also serve as a target, with their elimination through senolytics ameliorating early tumor growth and facilitating ICB-based immunotherapy [19, 23, 138]. Together, second-generation senolytics hold promise for attenuating senescence. Further clinical trials are needed to determine their safety and efficacy as cancer therapies.

Table 3: Preclinical studies clearing senescent immune and stromal cells within the tumor microenvironment.

Target	Treatment	Condition	Outcome	Reference
Neutrophil	3MRp16 model with ganciclovir suicide gene strategy	Prostate cancer	Suppressed tumor growth	[107]
	Procyanidin C1	Melanoma	Reduced tumor metastasis and restored T cell responses	[128]
Macrophage	Diphtheria toxin targeting tagged cells	Lung cancer	Diminished lung tumor burden and prolonged survival	[23]
	ABT-737			
	ABT-263	Lung cancer	Suppressed early tumorigenesis	[138]
	ABT-263	Colon cancer	Restored $CD8^+$ T cell proliferation and response to immunotherapy	[19]
	Nicotinamide mononucleotide	Glioblastoma	Inhibited T-cell dysfunction and delayed tumor initiation	[133]
	IL-4	Aging	Improved the health span of aged mice	[335]
T cell	Metformin	NA	Lowered IFN-γ and IL-6 and increased TNF-α production	[283]
	CD153-CpG vaccine	Obesity	Improved obesity-induced metabolic disorders	[333]
Endothelial cell	Anti-Notch1/ VCAM1 antibody	Ovarian cancer	Reduced tumor cell adhesion and lowered lung metastasis	[252]
	GPNMB vaccine	Atherosclerosis	Improved metabolic disorders	[334]
Fibroblast	ABT-199	Pancreatic cancer	Restored $CD8^+$ T cell function and response to immunotherapy	[236]
	ABT-737	Breast cancer	Enhanced NK cell function and infiltration	[263]
	Anti-TSPAN8 antibody	Breast cancer	Resensitize the response to chemotherapy	[237]
	Q	Osteosarcoma	Reduced tumor invasiveness	[303]

	D plus Q	Ovarian cancer	Reduced tumor metastasis	[304]

D, dasatinib; Q, quercetin; GPNMB, glycoprotein nonmetastatic melanoma protein B.

Finally, a therapeutic paradigm known as the "one–two punch therapy" has emerged, whereby induction of tumor-cell senescence is immediately followed by selective senolysis to maximize antitumor efficacy while limiting chronic SASP-driven toxicity [41, 43, 45]. In TP53-mutated liver cancer, inhibition of the DNA-replication kinase CDC7 specifically induced senescence of liver cancer cells, while subsequent treatment with mTOR inhibitors sertraline markedly reduced tumor growth [276]. The combination of 'one-two punch' therapy and immunotherapy has demonstrated potent inhibition of tumor growth in colorectal cancer and lung cancer [336, 337]. Ongoing efforts are identifying inducers and senolytics with enhanced specificity for senescent tumor cells to improve the therapeutic index [277, 337, 338]. Notably, perturbation of methionine catabolism precipitates DNA damage–mediated senescence in liver cancer cells, and follow-on senolytic therapy effectively attenuates hepatocarcinogenesis [58], suggesting that metabolic targeting may unlock a new frontier for precise, safe senescence induction.

8.4. Senescence reprogramming

Finally, since T cell exhaustion is reversible by ICB [177], researchers are exploring methods to revert cellular senescence. Opinions once held that no viable strategy had been identified to achieve this reversal, but recently, approaches have emerged to reverse senescence [339, 340]. Gu *et al.* showed that FBP1 suppression bypasses senescence in HCC progenitors, restoring their proliferative capacity [340]. Bi *et al.*

demonstrated that exosomes derived from human embryonic stem cells and their miR-302b content can reverse cellular senescence by targeting key cell cycle inhibitors, leading to rejuvenation in aging mice without safety concerns [339]. These two studies have unveiled the potential for reversing aging, raising anticipation for further research.

Moreover, the aged immune system can be reprogrammed to generate rejuvenated immune cells. First, one of the characteristics of natural immunosenescence is the involution of the thymus [48, 49], leading to reduced output of naive T cells. Efforts to rejuvenate the thymus have shown promise. Aged mice receiving IL-7 have shown enhanced adaptive immunity, as evidenced by lower viral load [341], while the thymostimulatory property of IL-21 was further demonstrated in the humanized mice model [342, 343]. Gene modulation targeting Foxn1 can also partially rescue thymic involution and reduction of peripheral $CD4^+$ T cells via exogenous FoxN1-cDNA [344], although recent research has indicated that Foxn1 overexpression does not prevent thymic involution [345]. The second approach is implementing hematopoietic transplantation. Through intrathymic injection of hematopoietic progenitor cells from healthy mice, thymic reconstitution could be achieved in mice with severe combined immunodeficiency [346]. Umbilical cord blood (UCB) can be an alternative source of HSCs [347]. Finally, $CD8^+$ T cells isolated from HIV patients can be reprogrammed to pluripotent stem cells, which subsequently re-differentiate into $CD8^+$ T cells with enhanced cytotoxicity and proliferation [348].

9. Conclusion and perspectives

In conclusion, senescence is a ubiquitous process affecting all components of the

TME. In this review, we highlighted that senescence extends beyond chronological aging, representing the sum of diverse senescence triggers. Aging can be understood as the cumulative effect of senescence inducers. In clinical settings, conventional and novel cancer therapies, oncogene-induced senescence, and interactions within the TME are significant contributors [54, 83-85]. This underscores the need for senescence studies to extend beyond just elderly populations.

Next, we have reviewed the properties of senescent immune cells in both innate and adaptive immunity, as well as the impact of SASP factors produced by senescent stromal cells. While adaptive and stromal senescence are well characterized, innate immune senescence in cancer remains understudied. This knowledge gap reflects the recent recognition of senescence in neutrophils and macrophages [50, 349]. As increasing studies have elucidated the roles of neutrophils and macrophages in tumor immunity [114, 121, 130, 134, 350-352], it becomes imperative to investigate the controversial role of innate immunosenescence in tumors.

Finally, we outline existing therapies targeting senescence. Though great progress has been made in targeting SASP and senescent cells, their clinical application remains distant, as discussed in the corresponding section above. Moreover, barriers to the clinical implementation of senescence-targeted therapy can be partly attributed to the classification of senescent cells in human samples, since it is essential for understanding how senescence influences responses to cancer therapy and clinical outcomes, and to what extent senescence-targeting therapy can benefit from cancer treatment [63]. Saleh *et al.* reviewed 21 studies that aimed to identify therapy-induced senescent cells in

patient samples [16] and highlighted current limitations, including limited approaches for senescence detection, the challenge of obtaining cancer samples from patients who have not undergone chemotherapy, the requirement for freshly frozen tissue for SA-β-gal staining, and variability in baseline expression of senescence markers across different cancer samples [16].

To address these challenges, it is urgently necessary to find solutions for the following issues: (a)To identify reliable inducers of senescence. Numerous factors can induce senescence, but identifying the most suitable one for laboratory and clinical conditions is crucial. Chemotherapy or radiation-induced senescence is not suitable for all tumor types, especially for those treated with chemotherapy after surgery [16]. Finding an inducer that works universally across cell types or matching various tumors with their viable inducers is essential. Typically, Scott W Lowe et al. have utilized T/P to induce senescence of pancreatic cancers and lung cancers [11, 87, 89]. However, a stable inducer for research on immunosenescence is still lacking. (b)To standardize existing markers. So far, SenNet has recommended senescence markers across different tissues of humans and mice [353]. Standard protocols exist for senescence research in vivo. According to the minimum information for cellular senescence experimentation in vivo (MICSE) published in 2024 [354], markers used to detect senescent cells should include at least three markers of different properties of cellular senescence, at least one of which should be increased $p16^{INK4a}$ or $p21^{Cip1/Waf1}$ expression. However, no standard has been established for clinical trials since MICSE is not intended for clinical practice. In breast cancers, progress is being made toward standardizing senescence detection,

including the establishment of baseline Lamin B1 expression and a three-marker signature approach to detect TIS, which involves downregulation of Lamin B1 and Ki-67 and upregulation of $p16^{INK4a}$ [355, 356]. (c)To discover emerging markers. Discovering specific markers will aid in understanding functional changes and targeting specific senescent cells. For instance, senescent cells can be isolated using flow cytometry by the differential presence of dipeptidyl peptidase 4 (DPP4) [357]. Anti-DPP4 antibodies enable natural killer (NK) cell-mediated elimination of senescent cells, offering new perspectives on senescence-targeted therapy [357]. CD153, differentially expressed in senescent T cells, could be applied as a vaccine to selectively clear senescent T cells in mice [333]. Moreover, advances in technology, such as artificial intelligence, high-throughput sequencing, and single-cell sequencing, offer new opportunities for studying senescence. For instance, uPAR, as one of the targets of CAR-T, was discovered with RNA-sequencing [87, 88]. Discovery of novel senolytics can now be achieved using machine learning [358]. Whether these new markers can be the next-generation markers in clinical practices remains to be validated. (d) To create novel detection approaches. Machine learning and artificial intelligence are gaining popularity in detecting senescence [353, 359], although identifying specific types of senescent cells remains challenging. Recently, Zhou *et al.* have introduced a brand-new approach to specifically trace certain types of senescent cells [360]. In this study, they generated pulse-chase tracing (Sn-pTracer), Cre-based tracing and ablation (Sn-cTracer), and gene manipulation combined with tracing (Sn-gTracer) to track $p16^{INK4a}$ macrophages and ECs, thereby enabling the clearance of specific types of senescent

cells [360]. It is believed that targeting senescent cells will become a reliable cancer therapy in the near future.

Abbreviations

SASP, senescence-associated secretory phenotype; DDR, DNA damages response; HSCs, hepatic stellate cells; PGE2, prostaglandin E2; HCC, hepatocellular carcinoma; OIS, oncogene-induced senescence; TME, tumor microenvironment; SA-βGal, senescence-associated ß-galactosidase; ECM, extracellular matrix; BM, bone marrow; TREM2, triggering receptor expressed on myeloid cells 2; APOE, apolipoprotein E; ADCC, antibody-dependent cellular cytotoxicity; NETs, neutrophil extracellular traps; NO, nitric oxide; FTO, fat mass and obesity-associated protein; EMT, epithelial-mesenchymal transition; APCs, antigen-presenting cells; FasL, Fas ligand; MDSCs, myeloid-derived suppressor cells; IMCs, immature myeloid cells; MO-MDSCs, monocytic myeloid-derived suppressor cells; PMN-MDSCs, polymorphonuclear myeloid-derived suppressor cells; TRAIL, TNF-related apoptosis-inducing ligand; NKCC, NK cell cytotoxicity; cDCs, classical dendritic cells; pDCs, plasmacytoid dendritic cells; CTLs, cytotoxic T lymphocytes; NSCLC: non-small cell lung cancer; ACKR2, atypical chemokine receptor 2; KLRG1, killer cell lectin-like receptor subfamily G 1; ICB, immune checkpoint blockade; PFS, progression-free survival; ADCP, antibody-dependent cellular phagocytosis; CDC, complement-dependent cytotoxicity; TLSs, tertiary lymphoid structures; LTi cells, lymphoid tissue inducer cells; HEVs, high endothelial venules; PMBCs, peripheral blood mononuclear cells;

CAFs, cancer-associated fibroblasts; iCAFs, inflammatory CAFs; myCAFs, myogenic CAFs; HDAC, histone deacetylase; PDAC, pancreatic ductal adenocarcinoma; ECs, endothelial cells; eNOS, endothelial nitric oxide synthase; CAR, engineered chimeric antigen receptor; SCAPs, senescent cells antiapoptotic pathways; D, dasatinib; Q, quercetin; UCB, umbilical cord blood; cAMP, cyclic adenosine monophosphate; ILT4,immunoglobulin-like transcript 4; TGF-β, transforming growth factor-β; HLA-G, human leukocyte antigen-G; PKA, protein kinase A; CREB, cAMP-response element binding protein; ATM, ataxia telangiectasia-mutated; ERK1/2, extracellular regulated protein kinases 1/2; STAT1/3, signal transducer and activator of transcription 1/3; CDK, cyclin-dependent kinases; Rb, retinoblastoma protein; TLR8, Toll-like receptors 8; GLUT, glucose transporter; MMP, matrix metalloproteinase; OPN, osteopontin; ECM, extracellular matrix; AREG, amphiregulin; ICAM-1, intercellular adhesion molecule-1; TNF-α, tumor necrosis factor-α; IL, interleukin; IFN-γ, interferon-γ; TGF-β, transforming growth factor-β; EVs, extracellular vesicles; VEGF, vascular endothelial growth factor; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; EMT, epithelial-mesenchymal transition; NK, natural killer; Th2, helper T cell 2; rDC, regulatory dendritic cell; IDO, indoleamine 2,3-dioxygenase; ABCB4, ATP-binding cassette subfamily B member 4; EphA2, erythropoietin-producing hepatocellular A2; ephrin-A1, recombinant human Ephrin A receptor 1; JAK, janus kinase; STAT, signal transducer and activator of transcription; NF-κB, nuclear factor-κB; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; STING, stimulator of interferon genes; mTOR, mammalian target of

rapamycin; MAPKAPK2, mitogen-activated protein kinase-activated protein kinase 2; DDR, DNA damage response; BCL-2, B-cell lymphoma-2; PI3K, phosphatidylinositide 3-kinases; CAR-T, chimeric antigen receptor-T; GPNMB, glycoprotein nonmetastatic melanoma protein B; uPAR, urokinase-type plasminogen activator receptor; NKG2DLS, Natural killer group 2 member D ligands; T/P, trametinib and palbociclib.

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Competing Interests

The authors declare that they have no competing interests.

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HZS, MMX and YYL collected the related studies and drafted the manuscript. XYL, JTN, CL, JH, QCM, WYW, WW and JX participated in the design of the review. XJY and SS initiated the study and revised the manuscript. All authors have read and agreed on the published version of the manuscript.

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