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Senescent immune cells in the tumor microenvironment: emerging insights into cancer immunotherapy resistance

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Cancer remains a leading cause of mortality worldwide, with rising incidence and death rates continuing to rise. While conventional treatments such as surgery, radiotherapy, and chemotherapy form the backbone of cancer care, they are often limited by adverse effects, recurrence risk, and incomplete tumor eradication. Tumor immunotherapy—particularly immune checkpoint inhibitors and chimeric antigen receptor (CAR) T cell therapy—has emerged as a transformative approach by activating and reprogramming anti-tumor immune responses. Despite these advances, significant challenges persist, including limited response rates to checkpoint inhibitors, the immunosuppressive nature of the tumor microenvironment (TME), and resistance mechanisms employed by tumor cells. Growing evidence suggests that immune cell senescence is a critical contributor to TME-driven immunosuppression. Senescent immune cells exhibit functional decline, elevated expression of inhibitory immune checkpoint molecules, and increased secretion of pro-inflammatory cytokines, collectively impairing anti-tumor immunity and reducing the efficacy of immunotherapy. This review highlights the role of immune cell senescence in shaping the immunosuppressive TME and driving resistance to immunotherapy. It further discusses emerging therapeutic strategies that combine immunotherapy with senescence-targeting interventions, aiming to provide novel insights into the development of more effective cancer treatment strategies.

KEYWORDS

tumor microenvironment, immune cell senescence, immunosuppression, cancer immunotherapy, anti-aging therapy, cancer treatment strategies

1 Introduction

According to recent reports, there were approximately 19.665 million new cases of malignant tumors and 9.737 million cancer-related deaths globally in 2022, with projections estimating up to 35 million new cases by 2050 (1). The lifetime risk of cancer-related death is estimated at approximately 11% for males and 8% for females. Advancements in detection technologies have significantly improved the accuracy of cancer diagnoses, further underscoring cancer's status as a leading cause of mortality worldwide (2–4). In parallel, population aging and lifestyle changes are expected to drive further increases in cancer incidence and mortality (5). Conventional cancer treatments—including radiotherapy, chemotherapy, and surgical resection—remain foundational but are often insufficient to achieve complete tumor eradication, thereby posing risks of recurrence. Additionally, these therapies are frequently associated with substantial side effects that adversely affect patient quality of life and long-term outcomes (6). For example, platinum-based chemotherapies are known to induce cardiotoxicity and nephrotoxicity, while other agents may cause peripheral neuropathy and a range of gastrointestinal complications (7). Moreover, the risk of tumor recurrence following surgical resection remains a significant concern (8). These limitations underscore the urgent need for more effective and durable therapeutic strategies.

Among emerging modalities, immunotherapy has gained prominence as one of the most promising and clinically impactful approaches in cancer treatment. Tumor immunotherapy—particularly immune checkpoint inhibition—aims to reinvigorate exhausted immune cells, reshape the tumor microenvironment (TME), and enhance the cytotoxic functions of effector T cells. For instance, immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 and its ligand (PD-1/PD-L1), as well as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), have demonstrated substantial clinical benefits in malignancies such as melanoma and non-small cell lung cancer (NSCLC), significantly improving overall survival (9). Chimeric antigen receptor T cell (CAR-T) therapy has also shown remarkable success in hematologic malignancies, such as acute lymphoblastic leukemia. However, its efficacy in solid tumors remains limited due to a range of barriers, although it continues to represent a breakthrough in cancer immunotherapy (10). Despite these advances, immunotherapy faces considerable challenges. Response rates to ICIs remain below 20% in many cancer types; some tumors exhibit an “immune desert” phenotype with poor immune cell infiltration, and tumor cells often develop resistance through multiple mechanisms, ultimately reducing treatment efficacy (11–13). Within the TME, immune cell senescence has emerged as a key contributor to immune dysfunction. Senescent immune cells typically exhibit impaired functionality, upregulation of immune checkpoint molecules such as PD-1, and increased secretion of pro-inflammatory cytokines. These features not only compromise anti-tumor immunity but also contribute to immunotherapy resistance, making immune senescence an increasingly important focus in cancer research (14, 15).

Immune cell senescence refers to the progressive decline in immune system function triggered by various stimuli, with cellular senescence as a central process. This state is characterized by a reduction in immune cell numbers, impaired effector functions, and diminished responsiveness to pathogens and tumor cells (16). Senescent immune cells exhibit hallmark features such as telomere shortening, oxidative damage, elevated levels of reactive oxygen species (ROS), DNA damage, increased expression of cell cycle regulators (e.g., p16^{INK4a} and p21^{CIP1}), and a senescence-associated secretory phenotype (SASP) marked by high levels of pro-inflammatory mediators. These changes collectively limit the cells' proliferative capacity and responsiveness to immunological challenges. In the TME, senescent immune cells—including T cells lacking expression of the co-stimulatory molecule CD28 (CD28[−] T cells)—exacerbate immune dysfunction, impairing anti-tumor responses and facilitating immune evasion by malignant cells (17, 18). Accumulating evidence indicates that these senescent cells not only fail to clear tumor cells effectively but may also promote tumor progression and metastasis through the secretion of immunosuppressive and pro-tumorigenic factors (19, 20). Once cancer is established, the presence of senescent immune cells severely compromises anti-tumor immunity, correlating with poor patient prognosis, reduced survival, and limited efficacy of immunotherapy.

This review discusses the mechanistic role of immune cell senescence in shaping an immunosuppressive TME, its contribution to immunotherapy resistance, and the therapeutic potential of combining immunotherapy with senolytic agents. Together, these insights aim to inform the development of novel strategies to enhance the efficacy of cancer immunotherapy.

2 Composition of the TME

The TME is a highly dynamic and complex ecosystem composed of malignant cells, diverse stromal and immune cell populations, extracellular matrix (ECM) components, and various bioactive molecules. The interplay among these components profoundly affects tumor initiation, progression, metastasis, and therapeutic responses.

2.1 Cellular components of the TME

2.1.1 Immune cells in the TME

The TME hosts innate and adaptive immune cells whose interactions determine tumor fate and treatment outcomes. Innate immune cells—including macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells—exhibit marked plasticity with context-dependent functions. M1 macrophages possess anti-tumor activity, whereas M2 macrophages promote immunosuppression, angiogenesis, and therapy resistance (21–23). Tumor-associated neutrophils polarize into N1 (anti-tumor) or N2 (pro-tumor) phenotypes; N1 reprogramming via interferon gamma (IFN- γ) conditioning has

shown therapeutic promise (24). NK cells eliminate tumor cells through cytotoxic mechanisms (25). Myeloid-derived suppressor cells (MDSCs), particularly polymorphonuclear (PMN)-MDSCs and monocyte (M)-MDSCs, inhibit T cell activity via contact-dependent (ROS/peroxynitrite) and independent (NO/arginase-1/cytokines) pathways, thereby promoting tumor progression (26–29). DCs serve as a bridge between innate and adaptive immunity by capturing tumor antigens and activating T cells. Subsets such as classical DC1 (cDC1) and CD103⁺ DCs are particularly important for effective anti-tumor immunity (30–32). Cancer-associated fibroblasts (CAFs) contribute to tumor progression by remodeling ECM, secreting immunosuppressive mediators, and promoting angiogenesis (33, 34).

Within the adaptive immune compartment, T cells play a central role in anti-tumor immunity. However, chronic antigen exposure and TME stress induce T cell exhaustion, characterized by impaired function and elevated expression of inhibitory receptors such as PD-1, CTLA-4—the primary targets of immune-checkpoint blockade (35–37). Regulatory T cells (Tregs) suppress effector T cell activity and sustain tumor-promoting immune tolerance (37). B cells exhibit dual roles: while capable of antibody production, antigen presentation, and tertiary lymphoid-structure formation, they also acquire regulatory functions or produce pro-tumor antibodies under TME influence, expanding MDSCs and dampening immunity (38–40). The functional states of all immune subsets are shaped by cellular crosstalk and metabolic competition within the TME. A comprehensive understanding of this immune-regulatory network is essential for developing effective cancer immunotherapies.

2.2 Non-cellular components of the TME

The non-cellular components of the TME—including soluble factors, the extracellular matrix (ECM), and exosomes—form a complex regulatory network that governs tumor progression and immune responses. Immunosuppressive cytokines, notably transforming growth factor beta (TGF- β), synergize with tumor-derived metabolic products to suppress T and NK cell functions, facilitating immune evasion. In contrast, interleukin (IL)-15 activates the janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, enhancing T and NK cell cytotoxicity while mitigating MDSC-mediated immunosuppression (41, 42), thereby remodeling the TME in favor of anti-tumor immunity. Pro-inflammatory cytokines like IFN- γ further augment anti-tumor responses by upregulating MHC expression (43–45). The complement cascade also contributes to immunosuppression, with activation fragments C3a and C5a recruiting and polarizing MDSCs, which subsequently secrete IL-10 and TGF- β to reinforce an immune-inhibitory milieu (46).

TGF- β -driven ECM remodeling, characterized by collagen deposition and matrix stiffening, induces epithelial-mesenchymal transition (EMT), enhances tumor invasion through biomechanical stress, and obstructs effector T cell infiltration (47–50). Exosomes play dual roles in TME regulation. Tumor-derived exosomes carry

PD-L1 and immunosuppressive miRNAs that systemically blunt immune activity, while immune cell-derived exosomes activate anti-tumor responses via MHC and co-stimulatory molecule delivery (51–55). Additionally, exosomal long non-coding RNAs (lncRNAs) contribute to immunosuppression by modulating immune checkpoint pathways, promoting M2 macrophage polarization, and suppressing NK and CD8⁺ T-cell activity (56). Collectively, these non-cellular elements orchestrate an immunosuppressive and pro-tumorigenic microenvironment, offering promising targets for biomarker development and innovative therapies such as exosome-based drug delivery systems.

2.3 Dynamics of the TME

The TME is a dynamic system wherein cellular and non-cellular components engage in continuous interaction through direct contact and paracrine/autocrine signaling, maintaining a shifting equilibrium. In early tumorigenesis, CD8⁺ T cells predominate, mediating tumor cell elimination via cytotoxic activity. As the tumor advances, the TME shifts toward an immunosuppressive state, enriched with MDSCs and Tregs. These cells suppress anti-tumor immunity by secreting inhibitory cytokines and expressing immune checkpoint molecules such as PD-1/PD-L1, thereby facilitating tumor growth and metastasis (57, 58). Tumor-derived metabolic byproducts, including lactate, further exacerbate immunosuppression and alter the physicochemical properties of the TME (59, 60). In later stages, increased angiogenesis and stromal remodeling further promote tumor dissemination and immune evasion (61).

Gastric adenocarcinoma (GAC) exemplifies TME plasticity, which critically influences tumor progression, immune escape, and therapeutic response (62, 63). IgA⁺ plasma cells dominate the pre-neoplastic mucosa, while stromal cells acquire a myofibroblast phenotype predictive of poor prognosis. As GAC progresses, there is a decline in activated CD8⁺ T cells and a corresponding rise in exhausted CD8⁺ T cells, Tregs, tolerogenic DCs, and pro-angiogenic endothelium. Metastatic niches are further characterized by immunosuppressive myeloid-derived CAFs. Two distinct TME ecotypes have been identified: EC3, enriched in CD4⁺/CD8⁺ T cells, NK cells, and DCs, is associated with responsiveness to ICIs, whereas EC6—marked by stromal expansion and dominance of IgG⁺ plasma cells—is linked to diffuse histology and ICI resistance (62). These findings underscore the importance of stage- and ecotype-tailored immunotherapeutic strategies in GAC.

2.4 Spatial heterogeneity of the TME

Spatial heterogeneity within the TME refers to region-specific differences in cellular composition, immune activity, and microenvironmental conditions within a single tumor—most notably between the tumor core and periphery. The tumor core often displays an “immune desert” phenotype, marked by hypoxia, metabolic stress, and accumulation of immunosuppressive factors,

which collectively restrict immune cell infiltration and promote immune tolerance (12, 13). In contrast, the tumor periphery typically harbors higher densities of effector immune cells, including CD8⁺ T cells and M1-polarized macrophages (64, 65). CD8⁺ T cells in the periphery secrete chemokine (C-C motif) ligand (CCL)3, CCL4, and CCL5, which recruit macrophages via C-C chemokine receptor type 5 (CCR5) signaling. These macrophages are subsequently polarized into the M1 phenotype by IFN- γ , enhancing CD8⁺ T cell cytotoxicity via inducible nitric oxide synthase (iNOS) and promoting antigen presentation (64). Nevertheless, even in the periphery, immune activity is shaped by local immunosuppressive signals, such as serum amyloid A1/2, C-X-C motif chemokine ligand 6 (CXCL6), creating a dynamic balance between activation and suppression (66). This spatial compartmentalization presents challenges and therapeutic opportunities. Strategies aimed at enhancing cytotoxic T cell infiltration and activity within the tumor core with amplifying M1 macrophage-mediated responses in the periphery, may offer synergistic benefits. Accordingly, detailed insights into spatial TME organization are crucial for optimizing immunotherapeutic design and predicting treatment outcomes. Recent advances in high-dimensional spatial profiling have elucidated the TME architectural complexity. In hepatocellular carcinoma, CO-Detection by indEXing (CODEX) has revealed that vimentin-high macrophages frequently co-localize with Tregs (67). These macrophages secrete IL-1 β , which enhances Treg-mediated immunosuppression by promoting IL-10 production and inhibiting CD4⁺ T cell proliferation, thereby facilitating immune evasion and disease progression (67). Targeting this macrophage subset may represent a promising strategy for personalized immunotherapy and prognostic refinement.

2.5 Temporal heterogeneity of the TME

The temporal heterogeneity of the TME reflects its dynamic evolution during tumor progression, as described by the three-phase cancer-immunity editing cycle (68). In the early elimination phase, the TME is immunologically “hot,” characterized by strong infiltration of effector T cells and NK cells, high IFN- γ levels, and efficient clearance of immunogenic tumor cells. Over time, the tumor enters an equilibrium phase, where immune pressure selects for clones with reduced immunogenicity, allowing tumor persistence. In the escape phase, the TME becomes immunosuppressive or “cold,” dominated by Tregs, MDSCs, M2 tumor-associated macrophages (TAMs), and elevated levels of IL-10 and TGF- β , facilitating immune evasion and therapy resistance. Notably, cellular senescence in tumor and immune cells critically shapes the immune-resistant TME across these stages.

In cervical cancer, high-risk HPV infection promotes carcinogenesis through sustained expression of E6 and E7 oncoproteins, which inactivate p53 and pRb, triggering oncogenic stress. This stress initially activates a senescence response via p15^{INK4b}, p16^{INK4a}, and p21^{Waf1/Cip1}, establishing a potent tumor-suppressive barrier by halting cell proliferation and inducing SASP-

mediated immune recruitment. However, continued E6/E7 expression disrupts senescence pathways, enabling a subset of cells to bypass arrest, attain immortality, and transition into the equilibrium phase. This progression supports a potential therapeutic strategy: re-inducing senescence in cancer cells followed by selective senolytic clearance. While conventional therapies can induce cancer cell senescence, they often simultaneously trigger senescence in TME-resident immune cells. The resultant SASP from senescent tumor and immune cells establishes a paracrine loop that reinforces immunosuppression and undermines anti-tumor immunity. Therefore, the development of strategies that prevent or reverse immune cell senescence in the TME is essential to optimize therapeutic efficacy.

3 Immune cell senescence in the TME

Aging is characterized by systemic, time-dependent immune deterioration, including thymic involution, reduced populations of naïve immune cells, chronic inflammation, and impaired antigen responsiveness (69). In contrast, immune cell senescence is a stimulus-induced state of irreversible cell cycle arrest, telomere attrition, and a SASP (70). This condition contributes to immune decline by promoting pro-inflammatory cytokine release and loss of cellular functionality. Notably, immune cell senescence can be induced within the TME independently of chronological age, playing a key role in shaping an immunosuppressive milieu.

3.1 Induction mechanisms of immune cell senescence

Immune cell senescence can arise through three primary mechanisms: intrinsic senescence, therapy-induced senescence, and TME stress-induced senescence, depending on the nature of the initiating stimuli.

- Intrinsic senescence is largely associated with aging and is driven by genomic instability, oxidative stress, and progressive telomere shortening. Over time, accumulated mutations impair DNA repair mechanisms, while excessive ROS generated during metabolism induce oxidative damage. Telomere attrition from repeated cell divisions ultimately triggers senescence signaling pathways, leading to immune dysfunction, chronic inflammation, and increased disease susceptibility (71).
- Therapy-induced senescence occurs in response to anticancer treatments such as chemotherapy and radiotherapy, which cause DNA double-strand breaks, ROS overproduction, and activation of inflammatory cascades (72). Chemotherapeutic agents—including topoisomerase inhibitors and alkylating agents—as well as targeted therapies such as cyclin-dependent kinase (CDK) inhibitors, Aurora kinase inhibitors, and epidermal growth factor receptor (EGFR) inhibitors, have been shown to

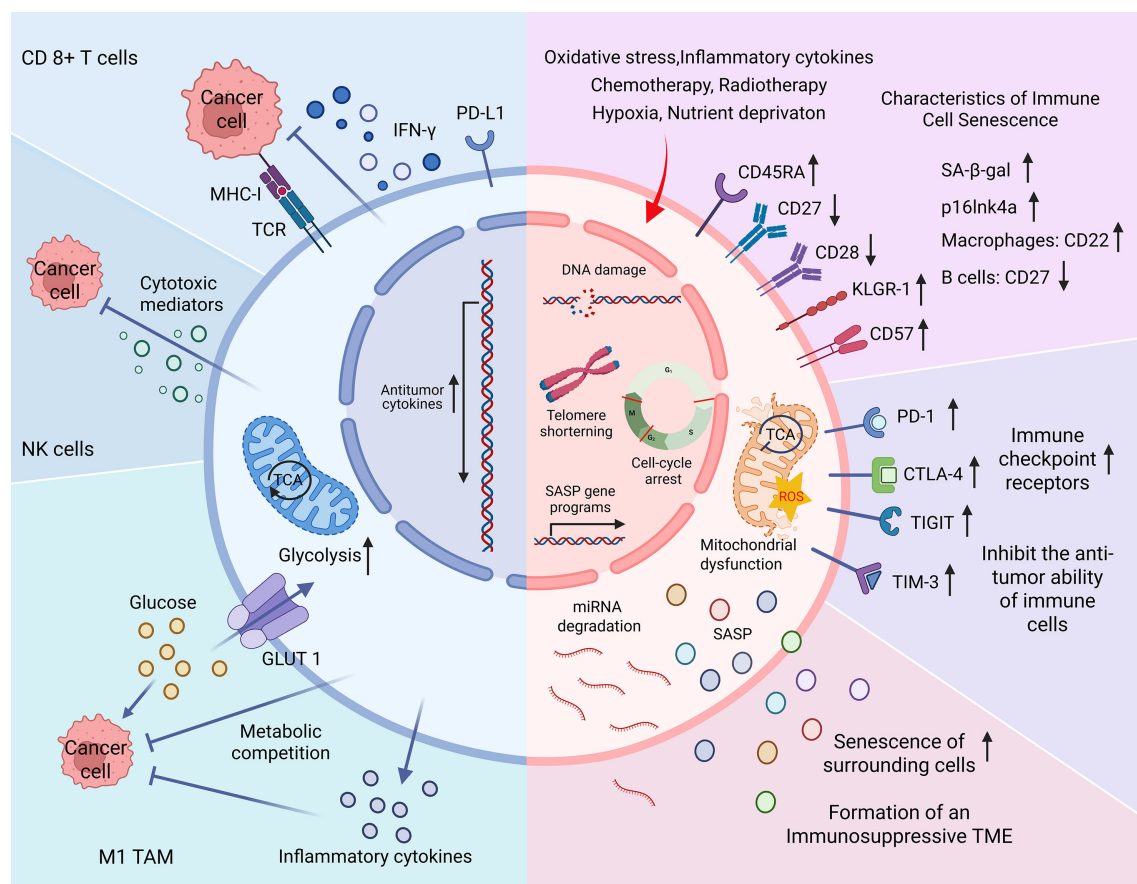


FIGURE 1

Characteristics of immune cell senescence in the tumor microenvironment (TME). The blue section (left) illustrates the antitumor functions of immune cells. Upon stimulation by major histocompatibility complex class I (MHC-I), CD8⁺ T cells secrete interferon-γ (IFN-γ), perforin, and granzymes to eliminate tumor cells. Natural killer (NK) cells similarly mediate tumor cell lysis by releasing cytotoxic molecules. M1-type tumor-associated macrophages (M1 TAMs) produce pro-inflammatory cytokines and compete with tumor cells for glucose, thereby inhibiting tumor growth through metabolic competition. The pink section (right) depicts the senescence of immune cells triggered by endogenous stress (e.g., oxidative damage), therapy-induced stress (e.g., chemotherapy), and TME-related factors (e.g., hypoxia). Senescent immune cells undergo DNA damage, telomere shortening, and cell cycle arrest. Phenotypic changes include downregulation of CD27 and CD28 and upregulation of CD45RA, CD57, and killer cell lectin-like receptor G1 (KLRG-1) in T cells. Common markers of senescence include increased senescence-associated β-galactosidase (SA-β-gal) activity and p16^{Ink4a} expression. Cell-type-specific alterations include CD22 upregulation in senescent macrophages and CD27 downregulation in B cells. Senescent immune cells also overexpress immune checkpoint receptors, leading to impaired cytotoxic responses. Additional features include mitochondrial dysfunction, microRNA degradation, and the secretion of senescence-associated secretory phenotype (SASP) factors. Together these changes contribute to the development of an immunosuppressive TME and diminished immunotherapeutic efficacy.

promote immune cells senescence in various cancers, including cervical, colorectal, and breast cancer (73–75).

- TME stress-induced senescence is triggered by harsh and metabolically hostile conditions within the TME. Environmental stressors such as hypoxia, nutrient deprivation, oxidative stress, and chronic exposure to inflammatory cytokines released by infiltrating immune and stromal cells activate stress-responsive signaling pathways and transcriptional programs. These ultimately lead to a senescent phenotype in immune cells (76).

Despite their distinct origins, all forms of immune cell senescence converge on common biological features: irreversible cell cycle arrest, impaired effector functions, SASP expression, and immunosuppressive reprogramming.

3.2 Characteristics of immune cell senescence

Immune cell senescence is characterized by a decline in the number and function of immune cells—particularly CD8⁺ T cells, NK cells, and B cells. This decline results in reduced responsiveness to pathogens, diminished vaccine efficacy, and heightened vulnerability to chronic diseases and cancer (Figure 1). In the TME, senescent T cells—especially CD45RA⁺ effector memory T cells re-expressing CD45RA (TEMRA cells)—are commonly observed. These cells typically show reduced expression of co-stimulatory molecules CD27 and CD28, along with increased levels of senescence markers such as CD57, killer cell lectin-like receptor G1 (KLRG-1), and senescence-associated β-galactosidase (77–79). Some terminally differentiated senescent CD8⁺ T cells also

partially express natural killer receptors (NKRs), enabling them to respond to antigens independently of T cell receptor (TCR) stimulation (80). In advanced gastric cancer, the expansion of NKR⁺ CD8⁺ T cells has been associated with more aggressive tumor phenotypes (81). Senescence in NK cells is marked by the downregulation of activating receptors and the upregulation of inhibitory receptors, which compromises their cytotoxic capacity against tumor cells (82).

A hallmark of immune senescence is the SASP, which consist of a diverse mix of bioactive molecules, such as pro-inflammatory cytokines (e.g., IL-1 β , IL-6, tumor necrosis factor alpha [TNF- α]), chemokines (e.g., CCL2, CXCL8), growth factors (e.g., vascular endothelial growth factor [VEGF], hepatocyte growth factor), and matrix metalloproteinases (MMPs) (83). SASP factors act through autocrine and paracrine mechanisms—supporting tissue repair and clearance of damaged cells on one hand, while on the other hand reshaping the TME and promoting tumor progression in malignancies such as lung and pancreatic cancer (84–87). The dynamic and heterogeneous composition of the SASP underlies its dual function, contributing to either immune stimulation or suppression depending on local microenvironmental cues.

Senescent immune cells also undergo profound epigenetic and metabolic reprogramming. Epigenetically, these cells display altered DNA methylation patterns at specific CpG sites, which impact the expression of genes central to immune function (88). Additionally, histone modification changes and non-coding RNA dysregulation further influence their transcriptomic profiles. Senescent T cells—key effectors in anti-tumor immunity—undergo marked epigenetic remodeling characterized by hypermethylation of gene-silencing CpG sites, repressive histone marks (e.g., H3K27me3, H3K9me3), and hypomethylation in flanking genomic regions (16). Crucially, promoter methylation of genes such as CD27 and SATB1 correlates inversely with their expression, directly impairing T cell functionality. The resultant nuclear landscape, including senescence-associated heterochromatin foci (SAHF), globally elevated chromatin accessibility, and depletion of linker histone H1, severely impairs anti-tumor activity. Moreover, in the CD28[−] T cell subset, miR-24 overexpression reduces H2AX expression, further impairing DNA damage repair and exacerbating T cell dysfunction (89). To the best of our knowledge, the use of epigenetic-modulating drugs to target immune cell senescence within the TME remains unexplored. This approach holds promise as a potential strategy for enhancing antitumor immunity and warrants further investigation as a future research direction.

Metabolically, senescent immune cells exhibit enhanced glycolytic flux, mitochondrial dysfunction, and elevated ROS levels—indicative of metabolic reprogramming that favors oxidative stress and further reinforces the senescent state (90, 91). Notably, epigenetic and metabolic alterations are interconnected: ROS accumulation can affect the activity of DNA methyltransferases, while aberrant methylation can dysregulate mitochondrial gene expression, forming a self-perpetuating loop of immune dysfunction.

In summary, senescent immune cells significantly reshape the immune landscape within the TME. By fostering an immunosuppressive environment and undermining anti-tumor responses, they contribute to tumor progression and reduced responsiveness to immunotherapy (Figure 2). Understanding the mechanisms underlying immune cell senescence and devising strategies to counteract these processes hold promise for enhancing the efficacy of cancer immunotherapy.

3.3 T cell senescence and the formation of an immunosuppressive TME

T cell senescence plays a pivotal role in tumor progression through a bidirectional relationship with TME remodeling. While T cell exhaustion and senescence contribute to tumor immune evasion, they are mechanistically distinct. Exhaustion results from chronic antigen exposure and is marked by high expression of inhibitory receptors (e.g., PD-1, CTLA-4), but remains reversible with immunotherapy. In contrast, T cell senescence is driven by cumulative stress and damage, leading to irreversible cell cycle arrest. Importantly, senescent T cells exert paracrine effects that amplify immunosuppression within the TME undermining immunotherapeutic efficacy.

Upon antigen stimulation, naïve T cells undergo TCR rearrangement and metabolic reprogramming involving glucose, glutamine, and fatty acid metabolism. These processes, initiated by antigen-presenting cell (APC) signals and regulated by CD28 the mammalian target of rapamycin complex (mTORC), support activation, proliferation, and differentiation into effector T cells (92, 93). Age-associated CD28 downregulation contributed to reduced generation of CD4⁺/CD8⁺ effector T cells, partially explaining immune deficits in aging and cancer.

Within the TME, Tregs acquire metabolic adaptability through expression of Forkhead box P3 (Foxp3) and sterol O-acyltransferase 2 (SOAT2), which suppress Myc-driven glycolysis and promote oxidative phosphorylation and cholesterol metabolism, facilitating their expansion (94, 95). By competing with effector T cells for glucose, Tregs trigger protein kinase B (AKT)-mediated DNA damage and activate senescence-related pathways (p21, p16, p53, and STAT1/3), leading to T cell senescence (91, 96, 97). Glucose deprivation also induces the mitogen-activated protein kinase (MAPK) cascade, p38 autophosphorylation, further promoting DNA damage and senescence (76). Additionally, $\gamma\delta$ Tregs directly induce senescence in naïve, effector T cells and DCs, acquiring potent immunosuppressive capacity (98, 99). While cytotoxic $\gamma\delta$ T effectors (encompassing $\gamma\delta$ T1 and $\gamma\delta$ T17) can promote tumor progression in response to TME stressors like hypoxia and metabolites, it is unknown if they share the capacity of $\gamma\delta$ Treg cells to induce immune cell senescence, a question that warrants further investigation (100, 101). *In vivo* studies show that Tregs can induce senescence in adoptively transferred tumor-specific T cells, thereby impairing the efficacy of CAR-T cells in melanoma models (102). In breast cancer, blockade of PD-L1 and/or STAT3 signaling

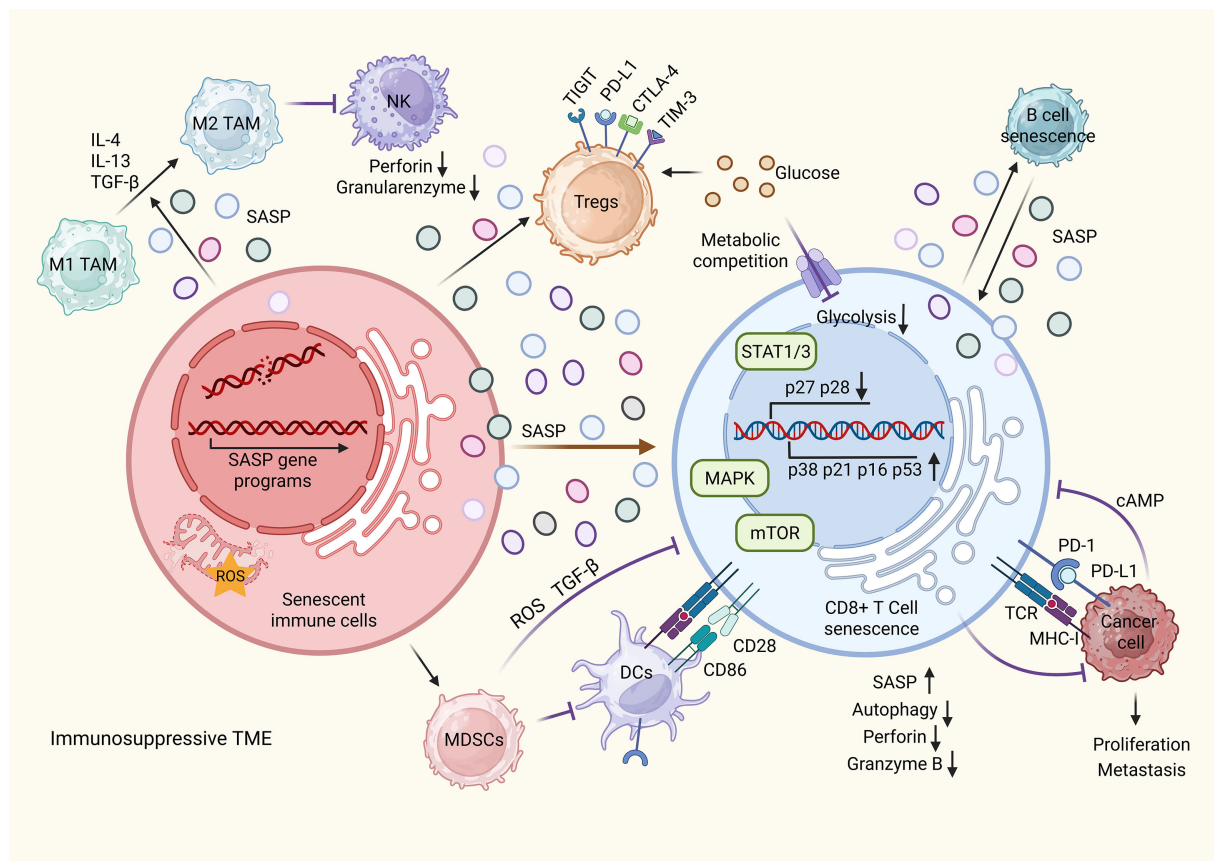


FIGURE 2

Immune cell senescence drives the formation of an immunosuppressive tumor microenvironment (TME). Senescent immune cells within the TME secrete senescence-associated secretory phenotype (SASP) factors that recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). These senescent cells can also induce senescence in neighboring immune cells, further amplifying SASP production. SASP factors and immune checkpoint molecules expressed by Tregs and MDSCs activate transcription factors such as mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 1/3 (STAT1/3), while concurrently suppressing the mammalian target of rapamycin (mTOR) signaling pathway in CD8⁺ T cells. This dysregulation leads to reduced expression of CD27 and CD28, alongside increased levels of p38, p21, p16, and p53, thereby promoting CD8⁺ T cell senescence. Senescent T cells exhibit impaired autophagy, diminished secretion of perforin and granzyme B, and loss of cytotoxic activity. These effects are exacerbated by elevated cyclic AMP (cAMP) levels resulting from altered tumor metabolism and nutrient competition, especially for glucose, between Tregs and effector T cells. MDSCs further suppress antitumor immunity by inhibiting antigen presentation through recruitment of dendritic cells (DCs). Additionally, SASP components drive the polarization of macrophages from the pro-inflammatory M1 to the immunosuppressive M2 phenotype and impair NK cell-mediated cytotoxicity. Together, these senescence-driven changes facilitate immune evasion, support the development of an immunosuppressive TME, and promote tumor growth and metastasis.

prevents $\gamma\delta$ Treg-induced senescence, enhancing the human epidermal growth factor receptor 2 (HER2)-specific responses and immunotherapy efficacy (99).

TME-derived metabolic byproducts, such as cyclic AMP (cAMP) and adenosine, further exacerbate T cell senescence. Tumor cells transfer intracellular cAMP to effector T cells via gap junctions, inducing DNA damage and accelerating senescence (103). Chronic exposure to extracellular adenosine suppresses telomerase, upregulates caspase-3, and downregulates CD28 by inhibiting its promoter, aggravating T cell aging (104). Senescent T cells also overexpress PD-1, which disrupts TCR signaling by inhibiting zeta-chain-associated protein kinase 70 (ZAP70) phosphorylation and the PI3K–AKT–mTOR axis, while activating p38 signaling (105). These changes impair autophagy and promote the accumulation of dysfunctional, senescent T cells in the TME. Functionally, senescent T cells express reduced levels of perforin

and granzyme B, diminishing their cytotoxicity (106–108). In summary, the immunosuppressive TME promotes T cell senescence, which in turn reinforces immune escape and therapeutic resistance. Disrupting this cycle by targeting senescence-associated pathways and restoring effector T cell function represents a promising strategy for improving immunotherapy outcomes.

3.4 Senescence of other immune cells and the formation of an immunosuppressive TME

Beyond effector T cells, the senescence of other immune cells—including macrophages, DCs, NK cells, and neutrophils—plays a significant role in shaping an immunosuppressive TME.

Macrophages, which may constitute up to 50% of the tumor mass, are particularly susceptible to premature senescence under conditions such as oxidative stress, DNA damage, and chronic inflammation (109). Senescent macrophages suppress T cell-mediated antitumor immunity, reduce the efficacy of ICIs, chemotherapy, and radiotherapy, and are associated with treatment resistance (110, 111). Notably, their experimental depletion enhances tumor control (112). Tumor-resident DCs, especially the CD103⁺ subset, are critical initiators of antitumor immunity and can potentiate responses to PD-L1 blockade while protecting against tumor rechallenge (32). However, Tregs can induce DC senescence through PD-L1 and STAT3 signaling, leading to impaired antigen presentation and diminished immunotherapeutic efficacy (99).

NK cells are key players in innate immunity, mediating tumor surveillance and orchestrating adaptive responses through the release of cytokines, chemokines, and growth factors (25, 113, 114). They recruit and activate DCs, indirectly enhancing T cell-mediated antitumor responses (25), and higher NK cell infiltration correlates with favorable prognosis in various cancer types (115, 116). Yet, in murine models of breast cancer and melanoma, senescent NK cells exhibit impaired cytotoxicity and disrupted glucose and lipid metabolism (117). Neutrophils are also similarly susceptible to TME-induced senescence. In prostate cancer, tumor-secreted apolipoprotein E promotes neutrophil senescence and accumulation of aged-like neutrophils with enhanced immunosuppressive activity (118). Altogether, the accumulation of senescent macrophages, DCs, NK cells, and neutrophils within the TME disrupts antigen presentation, suppresses cytotoxic lymphocyte function, and facilitates immune evasion. These alterations collectively contribute to resistance against multiple forms of cancer therapy, including ICIs, and underscore the need for senescence-targeted strategies to improve immunotherapeutic outcomes.

3.5 Dual role of SASP in regulating antitumor immunity

In addition to immune cells and their metabolic products, senescent cells within the TME contribute to tumor progression by transmitting senescence to neighboring cells through autocrine and paracrine mechanisms. SASP factors released by senescent T cells include a wide array of bioactive molecules, such as IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), proteases, growth and angiogenic factors, pro-inflammatory cytokines, MMPs, and components of extracellular vesicles (119–121). These molecules reinforce senescence in an autocrine fashion and modulate the behavior of adjacent tumor, stromal, and immune cells via paracrine signaling, thus remodeling the TME (121, 122). In certain contexts, SASP elements—particularly IL-1 α , IL-6, and IL-8—promote the recruitment of M1-like macrophages, Th1 cells, and NK cells, facilitating the clearance of senescent tumor cells and suppressing tumor progression (123). These findings highlight that senescence can, under specific conditions, support antitumor immunity. However, persistent accumulation of senescent cells

and chronic SASP secretion often lead to the establishment of an immunosuppressive, tumor-promoting environment. For example, aged fibroblasts injected into murine models secrete MMPs that degrade the ECM and release chemokines with pro-angiogenic and pro-tumorigenic activity, promoting tumor cell invasion and proliferation (122, 124). Additionally, SASP-derived IL-6 and IL-8 can drive EMT and enhance MMP expression, further contributing to metastasis (125–127). SASP components such as IL-6 also facilitate the recruitment of MDSCs into the TME. These cells suppress antitumor responses by producing arginase 1, TGF- β , and ROS, thereby inhibiting the activity of CD8⁺ T cells and NK cells (128, 129). Such mechanisms enable cancer cells—including those in breast cancer—to evade immune surveillance and expand despite immune pressure. In gastric cancer, TNF- α promotes the expansion of CD45RA⁺CCR7⁺ Treg subsets, which suppress CD8⁺ T cell function via STAT3 signaling (130). Senescent cell-derived exosomes also act as SASP vectors, carrying oncogenic cargo—including IL-6, mesenchymal-epithelial transition factor (MET), and pro-metastatic miRNAs—that activate PI3K/STAT3 and Wntless/Integrated (Wnt) signaling to drive proliferation, EMT, and angiogenesis. These vesicles may also deliver immunosuppressive molecules such as TGF- β , PD-L1, and ligands for natural killer group 2 member D, suppressing DC maturation and NK/CD8⁺ T cell cytotoxicity. Moreover, they can transfer oncogenic factors like human telomerase reverse transcriptase (hTERT) mRNA, Δ Np73, and cytoplasmic DNA, which promote chromosomal instability and chemoresistance (131, 132). This exosome-mediated communication further establishes a secondary SASP response in recipient cells, sustaining an inflammatory, immune-suppressive, and tumor-supportive niche. Additionally, senescent B cells expressing p16^{Ink4a} contribute to poor immunotherapy responses, as observed in bladder cancer. These cells activate p38/MAPK signaling and secrete SASP factors that further suppress antitumor immunity (133, 134). Overall, the influence of SASP on tumor immunity is highly context-dependent. While transient SASP activity in early tumorigenesis may enhance immunosurveillance and tumor suppression, persistent SASP signaling in advanced disease promotes tumor progression and immune evasion (135). Therefore, a nuanced understanding of the spatiotemporal dynamics of SASP is essential. Therapeutic strategies that selectively attenuate the chronic, pro-tumorigenic aspects of SASP while preserving its acute antitumor effects could significantly enhance the efficacy of immunotherapies.

4 The limitations of immune cell senescence on immunotherapy applications

Cancer immunotherapy, which aims to harness the immune system to eliminate tumors and prevent relapse, has revolutionized clinical cancer treatment. Major strategies include ICIs, cell-based immunotherapies, cancer vaccines, and immune modulators (Table 1). These approaches share a common goal: to remodel

TABLE 1 Overview of immunotherapy drugs: clinical use and ongoing trials.

Name	Clinical stage	Applicable tumors	Mechanism of action	Current limitations	References
PD-1/PD-L1 inhibitors					
Pembrolizumab	FDA-approved	NSCLC, Melanoma, etc.	Blocks PD-1/PD-L1 pathway, restoring T cell cytotoxic function	Poor response in low-mutational-load tumors	(237–239)
Nivolumab	FDA-approved	HCC, NSCLC, etc.	Blocks PD-1/PD-L1 pathway	irAEs; requires long-term monitoring	(237–239)
Atezolizumab	FDA-approved	TNBC, Urothelial Carcinoma	Blocks PD-1/PD-L1 pathway	May cause fatigue, rash	(237–239)
CA-170	Phase II Clinical Trial	Multiple solid tumors	Dual inhibition of PD-L1 and VISTA immune checkpoints	irAEs	(240)
CTLA-4 inhibitors					
Ipilimumab	FDA-approved	Metastatic Melanoma	Blocks CTLA-4, enhancing T cell activation	Diarrhea/colitis	(241)
Tremelimumab	Phase III Clinical Trial	HCC, Biliary Tract Cancer	Combined targeting of PD-L1 and CTLA-4, activating T cells	Limited efficacy as monotherapy	(242)
LAG-3 inhibitors					
Relatlimab	FDA-approved	Melanoma (combined with nivolumab)	Blocks LAG-3, enhancing T cell infiltration	Fatigue, rash	(243)
TIGIT Inhibitors					
Tiragolumab	Phase III Clinical Trial	NSCLC,SCLC	Blocks TIGIT-CD155 interaction, reversing T/NK cell inhibition; combines with PD-L1 inhibitors	Efficacy dependent on PD-L1 expression; mixed clinical outcomes	(244, 245)
Vibostolimab	Phase II/III Clinical Trial	NSCLC, Melanoma	Blocks TIGIT-CD155 pathway	Efficacy linked to PD-L1 status; common adverse events: pruritus, hypoalbuminemia	(244, 245)
TIM-3 inhibitors					
Sabatolimab	Phase III Clinical Trial	MDS, AML	Blocks TIM-3 binding to ligands, reversing T cell exhaustion; combinable with PD-1 inhibitors	Hematologic toxicity; limited monotherapy efficacy	(246)
Sym023	Phase I/II Clinical Trial	Advanced Solid Tumors, Lymphoma	Blocks TIM-3 pathway	Fatigue, infusion reactions	(247)
ACT therapies					
CAR-T Cell Therapy	FDA-approved	Large B-cell Lymphoma, Leukemia	Genetically engineered T cells targeting tumor antigens	Limited efficacy in solid tumors; off-target toxicity; CRS	(248)
Lifileucel	FDA-approved	Advanced Melanoma, Cervical Cancer	Expands TILs for reinfusion	Complex logistics; high toxicity	(249–251)
Ad-RTS-hIL-12	Phase I/II Clinical Trial	Melanoma, Brain Tumors	TIL-mediated IFN- γ production	High toxicity; risk of genomic integration	(252)
Other therapeutic agents					

(Continued)

TABLE 1 Continued

Name	Clinical stage	Applicable tumors	Mechanism of action	Current limitations	References
T-VEC	FDA-approved	Melanoma	Lyses tumor cells, activating APCs	Limited applicability	(248)
Sipuleucel-T	FDA-approved	Prostate Cancer	Delivers tumor antigens to activate T cells	Complex manufacturing; high cost; restricted usage	(248)
Tebentafusp	FDA-approved	Melanoma	Engineered TCR targeting gp100 antigen, activating T cells	High cost; narrow applicability	(251)
KN046	Phase II Clinical Trial	HCC, NSCLC	Simultaneously blocks PD-L1 and CTLA-4, enhancing synergistic effects	Dual targeting may increase risk of irAEs	(253)
Oleclumab	Phase I/II Clinical Trial	TNBC	Inhibits CD73-mediated adenosine production, alleviating immunosuppressive microenvironment	Fatigue, diarrhea	(254)

PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; LAG-3, Lymphocyte-activation gene 3; TIGIT, T-Cell immunoreceptor with Ig and ITIM domains; TIM-3, T-Cell immunoglobulin and mucin-domain containing-3; VISTA, V-domain Ig suppressor of T cell activation; CD73, Cluster of differentiation 73; ACT, Adoptive cell transfer; CAR-T, Chimeric antigen receptor T cell therapy; TIL, Tumor-Infiltrating lymphocytes; TCR, T cell receptor; APCs, Antigen-presenting cells; Treg, Regulatory T Cells; NK, Natural killer; IFN- γ , Interferon gamma; CRS, Cytokine release syndrome; NSCLC, Non-small cell lung cancer; HCC, Hepatocellular carcinoma; TNBC, Triple-negative breast cancer; SCLC, Small cell lung cancer; AML, Acute myeloid leukemia; MDS, Myelodysplastic syndromes; irAEs, Immune-related adverse events; gp100, Glycoprotein 100; FDA, Food and Drug Administration.

the TME and enhance effector T cell function. However, the accumulation of senescent immune cells within the TME poses a significant barrier to immunotherapy efficacy. These senescent cells contribute to immune dysfunction, reduce cytotoxic responses, and propagate immunosuppressive signaling, thereby undermining therapeutic outcomes. Consequently, a deeper understanding of immune cell senescence within the TME is critical to overcoming resistance and optimizing the benefits of immunotherapy. Integrating senolytic agents or anti-senescence strategies with existing immunotherapies may provide a promising avenue to eliminate dysfunctional immune cells or restore their function. Such combinatorial approaches could help overcome immunotherapy resistance and enhance the efficacy and durability of treatment responses.

4.1 Immune checkpoint inhibitors

Immune checkpoints are inhibitory receptors on T cells exploited by the TME to suppress anti-tumor immunity and promote exhaustion. Immune checkpoint inhibitors (ICIs) block these pathways, restoring T cell function and revolutionizing cancer treatment, with efficacy in melanoma, NSCLC, renal cell carcinoma, and triple-negative breast cancer, though resistance remains a challenge (136–139). Key checkpoints include PD-1, which attenuates T cell signaling upon binding PD-L1, and CTLA-4, which inhibits T cell activation by competing with CD28 (140, 141). Clinically approved ICIs—such as pembrolizumab, nivolumab, and ipilimumab—have demonstrated significant benefit in multiple cancer types. To overcome resistance, combination therapies—such as dual checkpoint blockade (e.g., PD-1 plus CTLA-4) or pairing ICIs with chemotherapy, radiotherapy, or targeted agents—are being actively tested. Novel checkpoints like lymphocyte activation gene-3 (LAG-3), T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT), and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) also play non-redundant roles in immunosuppression; while monotherapies against them have limited efficacy, combinations with PD-1 blockade show enhanced anti-tumor responses (142–151). For example, the LAG-3 inhibitor relatlimab combined with nivolumab is U.S. Food and Drug Administration (FDA)-approved for melanoma, while TIGIT and TIM-3 inhibitors are primarily being evaluated in combination with PD-1 inhibitors (152–154). Ongoing studies are exploring dual or multi-modal regimens to overcome resistance in solid tumors and expand the proportion of patients who benefit from immunotherapy.

4.2 Adoptive cell therapy

In recent years, ACT has emerged as a promising immunotherapeutic strategy to overcome T cell exhaustion within TME, encompassing approaches such as tumor-infiltrating lymphocytes (TILs), CAR-T cells, and TCR-engineered T cells.

TIL therapy involves expanding and reinfusing a patient's naturally tumor-reactive T cells, showing strong efficacy in melanoma but limited by complex manufacturing (155–157). CAR-T cells are genetically modified to target surface antigens independently of MHC, achieving remarkable success in hematologic malignancies but struggling in solid tumors due to poor infiltration and immunosuppression; next-generation constructs and alternative platforms like CAR-natural killer (CAR-NK) and CAR-macrophage (CAR-M) are being explored to enhance efficacy (158–162). TCR-T therapy, which engineers T cells to target MHC-presented intracellular antigens, offers deeper tumor penetration but is constrained by human leukocyte antigen (HLA) matching, off-target toxicity risks, and limited antigen availability (163–166). While ACT has shown substantial success in hematologic malignancies, its efficacy in solid tumors remains limited—largely due to immune aging and the immunosuppressive nature of the TME (167, 168). Therefore, future advances will likely rely on combinatorial strategies—such as improving cell persistence, developing novel constructs to resist the TME, and combining ACT with immune checkpoint blockade—to achieve broader and more durable anti-tumor responses.

4.3 Cancer vaccines

Cancer vaccines aim to activate the immune system to generate antigen-specific T cells that mediate tumor regression (169). Current efforts focus on neoantigen-based vaccines, which arise from somatic mutations and are uniquely expressed by tumor cells (170, 171). Unlike tumor-associated antigens, neoantigens are recognized as non-self, avoiding central tolerance and enabling the induction of high-affinity cytotoxic T lymphocytes with minimal off-target toxicity (172). This makes them ideal immunotherapy targets due to their high immunogenicity and tumor specificity. Personalized cancer vaccines (PCVs) are developed by sequencing tumor and matched normal samples to identify patient-specific neoantigens, which are then formulated into mRNA- or peptide-based platforms. These vaccines elicit targeted immune responses that selectively eliminate tumor cells while sparing normal tissues (173). Clinical trials have demonstrated that PCVs can reduce recurrence and prolong disease-free survival in high-risk patients, including those with renal cell carcinoma, with durable vaccine-specific T cell responses persisting over 36 months (174). The clinical efficacy of ICIs correlates with neoantigen burden (175, 176), supporting the combination of PCVs with ICIs to enhance outcomes. Despite progress, the efficacy of neoantigen vaccines (e.g., LK101 injection) is limited by the immunosuppressive TME (177–179). Factors such as Tregs, MDSCs, and immunosuppressive cytokines, along with vaccine-induced resistance, diminish PCV immunogenicity (180). Overcoming these challenges requires deeper understanding of the TME and strategies to modulate its immunosuppressive properties. Optimizing PCV design and clinical utility will depend on rational combination therapies, improved antigen selection, and real-time immune monitoring.

4.4 Immunotherapy resistance and immune cell senescence

Although immunotherapy has improved treatment response and safety relative to conventional chemotherapy, many cancers eventually develop resistance (11). This resistance is multifactorial, involving tumor-intrinsic and immune-related mechanisms. Among these, immune cell senescence and the resulting immunosuppressive TME contribute substantially to therapeutic failure. For instance, loss of HLA class I—a key mediator of antigen presentation—through genetic mutations or epigenetic silencing impairs tumor immune recognition (181, 182).

Clinical studies have shown that while PD-1 inhibitors improve survival in younger (<65 years) and older (≥65 years) patients, no survival benefit is observed in those aged ≥75 years compared to chemotherapy (183). Similarly, ICIs show limited efficacy in reversing T cell exhaustion in glioblastoma multiforme (GBM) (184). In NSCLC, elevated levels of circulating CD57⁺KLRG-1⁺ CD8⁺ T have been associated with poor ICI responses (185). Aged mouse models of melanoma have demonstrated reduced anti-PD-L1 efficacy due to impaired DC migration and diminished CD8⁺ T cell responses—effects that were partially reversed by DC activators (186). Likewise, triple-negative breast cancer models have shown deficient CD8⁺ T cell activation in aged mice, rendering ICIs ineffective (187). Similar patterns of age-related ICI resistance have been reported in colon cancer and lymphoma models (74). Senescent Tregs and MDSCs accumulate in the TME and suppress CD8⁺ T cells via IL-10, TGF-β, PD-1/PD-L1, and TIGIT/CD155 signaling pathways, further contributing to anti-PD-L1 therapy resistance. Moreover, metabolic dysfunction in senescent immune cells leads to upregulation of IDO activity, resulting in L-tryptophan depletion and accumulation of immunosuppressive metabolites such as N-formylkynurenine, which further attenuate antitumor immunity (188, 189).

Peripheral senescent T cells—often induced by chronic antigen exposure or extensive chemotherapy—can impair the function of adoptively transferred cells and reduce the efficacy of cancer vaccines. In melanoma models, senescent immune cells have been shown to diminish CAR-T cell efficacy (102). Preconditioning T cells to mitigate senescence-associated phenotypes can improve the specificity and durability of ACT therapies. For instance, engineering CAR-T cells with dual co-stimulatory domains (CD28 and 4-1BB) enhances metabolic fitness and resistance to senescence, resulting in improved antitumor responses (190). Co-treatment with CAR-NK and CAR-T cells in multiple myeloma has been shown to restore co-stimulatory molecule expression and delay T cell senescence (191). Similarly, early Phase III trial data for CimaVax-EGF, a therapeutic vaccine for stage IIIB/IV NSCLC, suggest reduced efficacy in the context of T cell senescence (192). Furthermore, the effectiveness of neoantigen vaccines depends on a stable and diverse TCR repertoire, which is often compromised in aged or senescent immune systems. In summary, immune cell senescence promotes the development of a suppressive TME and contributes to immunotherapy resistance through multiple mechanisms.

Cancer stem cells (CSCs) are now recognized as primary drivers of therapeutic resistance to immunotherapy (193). By downregulating MHC class I, NKG2D ligands, and neoantigens, CSCs reduce their immunogenicity. Concurrently, they secrete immunosuppressive cytokines such as TGF- β , IL-6, and CCL2/CCL5 to recruit M2-polarized TAMs, MDSCs, and Tregs, while upregulating “don’t-eat-me” signals—including PD-L1, CD47, and CD155—to inhibit cytotoxic T cell, NK cell, and macrophage responses (194, 195). Their intrinsic plasticity allows CSCs to enter slow-cycling or EMT-mediated dormancy states, enabling rapid phenotypic switching under immune pressure. This adaptability constructs a highly immunosuppressive, low-immunogenic, and cytotoxic escape network. Although direct evidence linking CSCs to immune cell senescence remains limited, the functional overlap between CSC-mediated immune evasion and senescence-associated immune dysfunction suggests potential crosstalk between CSCs and senescent immune cells. Together, they may synergistically shape an immunosuppressive TME and contribute to resistance against immune-based therapies. Addressing senescence-associated immune dysfunction may therefore be critical to overcoming resistance and enhancing the long-term efficacy of cancer immunotherapy.

4.5 Special considerations for immunotherapy in elderly cancer patients

Aging induces structural and functional changes in immune organs such as the thymus, bone marrow, spleen, and lymph nodes, resulting in impaired immune surveillance, reduced antigen presentation, accumulation of immunosuppressive Tregs and memory lymphocytes, and diminished cytotoxic CD8⁺ T cell responses (196–199). These age-associated immune alterations significantly limit the efficacy of immunotherapy in elderly patients. Although some studies report elevated PD-L1 expression in older individuals, its predictive value for immunotherapy response remains inconclusive (200, 201). Compared to younger patients, the elderly exhibit more pronounced immune cell senescence, contributing to tissue degeneration, comorbidities, and a systemic pro-inflammatory state driven by SASP. This chronic inflammation exacerbates T cell exhaustion and senescence, increases tumor susceptibility, and dampens immunotherapeutic responses (202). For example, Huff et al. reported increased levels of senescent T cells in the TME and peripheral blood of patients with GBM, indicating systemic impairment of immune responses (184). Age-related changes in the TME also hinder immunotherapy efficacy. In aged mice, altered immune cell composition—particularly enhanced emergency myelopoiesis—accelerates lung tumor progression. IL-1 α is upregulated in lung tumors of older mice, promoting myelopoiesis and immunosuppression. Notably, blockade of IL-1 α signaling delayed tumor growth and enhanced NK cell-mediated immunity (203).

ICIs, while beneficial, are associated with immune-related adverse events (irAEs), which can cause multi-organ toxicities

and reduce treatment tolerance. These events are thought to result from reactivation of autoreactive T cells. Advanced age is a known risk factor for irAEs, with frail older adults experiencing higher rates of hospitalization, longer hospital stays, and more frequent ICI discontinuation (204). Despite the increasing use of ICIs in clinical practice, elderly individuals remain underrepresented in clinical trials, limiting available safety and efficacy data for this population. Therefore, further research is essential to determine the risk–benefit ratio of immunotherapy in older adults.

5 Combined therapeutic strategies: senolytics and immunotherapy

Cellular senescence serves as a double-edged sword in cancer biology. In the precancerous phase, clearing senescent cells using immunotherapy or senotherapeutics can prevent tumor initiation—particularly beneficial in the elderly, where senescent cell accumulation and SASP contribute to a pro-tumorigenic microenvironment. However, in established tumors, anti-cancer therapies and metabolic stress can induce detrimental senescence in immune cells, fostering an immunosuppressive TME that undermines the effectiveness of immunotherapy. Strategically timed combinations of senotherapeutics and immunotherapy offer promising avenues to restore anti-tumor immunity and enhance therapeutic outcomes. However, the timing of senescence-targeting intervention is critical: interventions introduced too early may disrupt therapy-induced tumor suppression, while delayed application may allow irreversible SASP-mediated damage to accumulate. This highlights the urgent need for precise biomarkers that can guide the optimal timing of intervention. Additionally, developing targeted senotherapeutics capable of selectively eliminating harmful senescent cells—while sparing beneficial ones such as functionally recovering immune cells or quiescent stem cells—remains a vital complementary strategy (Table 2).

5.1 Potential of anti-aging drugs as adjuvants in antitumor therapy

Metformin, a traditional antidiabetic agent, has emerged as a promising candidate with anti-aging and antitumor properties (205). It inhibits mitochondrial complex I and mTOR signaling, thereby lowering systemic glucose utilization, enhancing CD8⁺ T cell-mediated tumor clearance, and improving the efficacy of anti-PD-1 immune checkpoint blockade (206). By suppressing glycolytic metabolism, metformin also facilitates the development of memory T cells, further strengthening long-term antitumor immunity (207). Multi-omics analyses of Treg metabolism suggest that targeting shared metabolic pathways between Tregs and tumor cells can disrupt Treg homeostasis and phenotypic stability. This strategy offers a selective and controllable approach for depleting Tregs within the TME (208).

TABLE 2 Anti-senescence agents used in combination with immunotherapy.

Drugs	Therapeutic target	Clinical/preclinical applications	Combination product	NCT number or References
Metformin	mTOR and Complex I	Cervical, Vaginal, and Vulvar Cancers; Phase II	HPV Vaccine and Imiquimod	NCT06686043
		Refractory Microsatellite Stable Metastatic Colorectal Cancer; Phase II	Nivolumab	NCT03800602
		Stage III-IV Non-small Cell Lung Cancer That Cannot Be Removed by Surgery; Phase II	Nivolumab	NCT03048500
		Small Cell Lung Cancer; Phase II	PD-1 inhibitor (Sintilimab)	NCT03994744
		Metastatic Breast Cancer and Triple-negative Breast Cancer; Phase II	EGCG, Quercetin, and zinc	NCT05680662
Quercetin	Oxidative Stress	Metastatic Breast Cancer and Triple-negative Breast Cancer Phase II	Epigallocatechin gallate, Metformin, and zinc	NCT05680662
Dasatinib		Metastatic Melanoma; Phase II	Dendritic Cell Vaccines	NCT01876212
		B-cell Acute Lymphoblastic Leukemia; Phase III	Chemotherapy and Blinatumomab	NCT06124157
Rapamycin	mTOR	NY-ESO-1 Expressing Solid Tumors; Phase I	Vaccine Therapy	NCT01522820
		Relapsed and Refractory Multiple Myeloma; Phase Ib	Pomalidomide, and Dexamethasone	NCT03657420
		PD-(L)1 Resistant Solid Tumors; Phase I/II	Autologous Rapamycin-Resistant Th1/Tc1 Cell Therapy	NCT05144698
Everolimus		Colorectal Cancer; Phase	PD-1	NCT06301386
Temsirolimus		Advanced or Metastatic Malignancy; Phase I	Bevacizumab and Valproic Acid, or Cetuximab	NCT01552434
Ruxolitinib Phosphate	JAK2	Metastatic Stage IV Triple Negative Breast Cancer; Phase I	Pembrolizumab	NCT03012230
VTX-2337	TLR 8	Squamous Cell Carcinomas of the Head and Neck; Phase I	Cetuximab	NCT01334177
β-Glucan	MDSC	Lung Cancer; Phase II	Vaccine 1650-G	NCT01829373
ABT-263	BCL-2	Preclinical	-	(209–212)
ABT-737				
Resveratrol	NRF2	Preclinical	-	(215–218)
Digoxin	Na+/K+ pumps	Preclinical	-	(209–212)
Ouabain				
Cetuximab	IL-6	Preclinical	-	(220, 221)

The NCT numbers in the table are from the ClinicalTrials website. mTOR, Mammalian target of rapamycin; HPV, Human papillomavirus; PD-1, Programmed cell death protein 1; EGCG, Epigallocatechin gallate; NY-ESO-1, New York Esophageal Squamous Cell Carcinoma 1; Th1, Helper T cell 1; Tc1, Cytotoxic T cell 1; JAK2, Janus kinase 2; Toll-like receptor 8; MDSC, Myeloid-derived suppressor cell; Bcl-2, B-cell lymphoma-2; NRF2, Nuclear factor erythroid 2-related factor 2; IL-6, Interleukin-6.

First-generation senolytic agents—including B-cell lymphoma-2 (Bcl-2) family inhibitors (ABT-263, ABT-737), dasatinib and quercetin combinations, and cardenolides (e.g., ouabain, digoxin)—have been successfully employed alongside radiotherapy and chemotherapy to eliminate therapy-induced senescent cells, thereby limiting tumor progression and metastasis (209–212). For example, Maggiorani et al. (74) demonstrated that combining the Bcl-2 inhibitor ABT-263 with immunotherapy enhances therapeutic efficacy by clearing senescent cells and restoring immune homeostasis within the TME, ultimately improving survival outcomes. Emerging senolytic strategies include

engineered CAR-T cells targeting senescent cell-specific surface markers. Urokinase-type plasminogen activator receptor (uPAR), commonly upregulated on senescent cells, has been exploited for uPAR-specific CAR-T cell therapies to selectively eliminate senescent cells *in vitro* and *in vivo*, leading to improved outcomes in mouse models of lung cancer and liver fibrosis (213). Additionally, recent work has identified bifunctional apoptosis regulator (BFAR) as a critical modulator enriched in senescent CD8⁺ T cells. BFAR restricts STAT1-mediated reprogramming of tissue-resident memory T cells by regulating JAK2 deubiquitination. Inhibition of BFAR using the small molecule

iBFA2 restores memory T cell generation and rescues antitumor activity in senescent or anti-PD-1-resistant CD8⁺ T cells (58). Collectively, senolytic agents offer a compelling strategy to enhance cancer immunotherapy by clearing senescent cells, reactivating immune effector functions, and mitigating the immunosuppressive effects of the TME. However, their application requires careful consideration of tumor type, therapeutic timing, and the patient's immune status to avoid off-target effects and optimize therapeutic benefit.

5.2 Development and challenges of SASP inhibitors

Given the critical role of SASP in promoting tumor progression and therapy resistance, targeting SASP presents a promising alternative to senolytics. This approach aims to mitigate the deleterious effects of persistent senescent cells while preserving their transient benefits in immunosurveillance (214). Key regulators of the SASP include the mTOR and NF- κ B pathways. Studies have shown that metformin (which inhibits NF- κ B nuclear translocation), rapamycin (an mTOR inhibitor), and resveratrol (an activator of the nuclear factor erythroid 2-related factor 2 [Nrf2] pathway) can suppress SASP expression, exerting anti-aging and anti-tumor effects (215–218). Notably, metformin has also been shown to enhance the efficacy of ICIs, highlighting its potential for cancer immunoprevention and treatment (219). Additionally, monoclonal antibodies targeting specific SASP factors have been explored. For example, cetuximab, an anti-IL-6 antibody, has been used to treat multicentric Castleman's disease and is currently under investigation in various cancer types (220, 221).

Despite these advances, the indiscriminate inhibition of SASP poses significant challenges. Cytokines such as IL-6 and IL-8 are essential for normal immune responses; their sustained suppression may compromise immune activation, increase susceptibility to infections, and disrupt immune homeostasis. Paradoxically, this could lead to chronic inflammation, immune tolerance, and impaired anti-tumor immunity. Moreover, the heterogeneity of the SASP complicates its clinical translation. SASP composition varies depending on tissue type, cellular origin, the nature of the senescence-inducing stimulus, and temporal context. For example, different senescence inducers in hepatocellular carcinoma elicit distinct SASP profiles: CX5461 predominantly induces the IL-8/CXCL10 axis, while alisertib upregulates VEGF (222). Even within the same tumor type, SASP signatures may differ due to genetic background, cell lineage, or donor variability (223). Therefore, the effective development of SASP inhibitors will require: selective targeting of tumor-promoting SASP components while preserving immune-activating elements; precision molecular strategies that integrate immune monitoring and patient-specific profiling; and combinatorial approaches with immunotherapies to maximize efficacy and minimize immunosuppression.

Ultimately, refining SASP modulation will be essential for translating this promising approach into safe and effective personalized cancer therapies.

5.3 Prospects of nanodelivery systems in combination therapy

Conventional immunotherapies and senotherapeutics are often hindered by systemic toxicity, poor pharmacokinetics, and limited specificity (224). Nanodelivery systems offer a promising solution by enhancing drug targeting, stability, and bioavailability. Surface modifications with antibodies, peptides, or ligands—such as folic acid or HER2—enable active targeting of tumor cells (225). Nanoparticles (10–100 nm) also exploit the enhanced permeability and retention effect of tumor vasculature for passive targeting. Additionally, nanocarriers protect therapeutic agents from enzymatic degradation, extend circulation time, and concentrate drugs at tumor sites, thereby minimizing off-target effects.

A variety of nanomaterials have been developed to enhance anti-aging and anticancer therapies. For example, mesoporous polydopamine nanoparticles coated with galactan and loaded with dasatinib and quercetin can respond to high β -galactosidase activity and acidic pH, effectively clearing chemotherapy-induced senescent cells and suppressing breast cancer progression and metastasis (226). Similarly, mPEG-PLGA-PLL nanoparticles (composed of methoxy polyethylene glycol, poly[lactic-co-glycolic acid], and poly-L-lysine) conjugated with PD-L1-blocking antibodies enhance early CD8⁺ T cell immunosurveillance, reverse T cell dysfunction, and prevent immune escape (227). Nanostructures incorporating tumor antigens have demonstrated therapeutic promise in preclinical models of melanoma, thymoma, and lymphomas. Once administered, these structures are preferentially internalized by DCs, which stimulates robust effector T cell and antibody responses, ultimately improving survival outcomes (228, 229). In cancer vaccine formulations, glycosylated PLGA nanoparticles have been employed to co-deliver ovalbumin and CpG oligonucleotides as adjuvants, enhancing immune activation (230). Another innovative approach involves magnetic nanoparticles (Fe₃O₄) loaded with sulfamethazine and cloaked with platelet membranes (Fe₃O₄-SAS@PLT). These induce ferroptosis in tumor cells while reprogramming M2-like macrophages into M1-like phenotypes, thereby disrupting the immunosuppressive TME and enhancing ICI efficacy (231). The integration of nanotechnology, cellular senescence modulation, and immunotherapy represents a cutting-edge direction for developing safer, more precise, and highly effective cancer treatments. This convergence holds significant potential for advancing personalized immunotherapy and overcoming current limitations in cancer therapy.

6 Conclusion and perspectives

The self-perpetuating feedback loop between senescent immune cells and the immunosuppressive TME represents a major obstacle to effective cancer immunotherapy. Senescent immune cells not only lose their intrinsic antitumor functions but also secrete SASP components—including IL-6, CXCLs, and IL-10—that recruit and activate immunosuppressive populations such as Tregs and

MDSCs, while promoting macrophage polarization toward the M2 phenotype. These effects collectively intensify immunosuppression within the TME. Conversely, TME-associated stressors such as hypoxia, metabolic reprogramming, and upregulated immune checkpoint signaling (e.g., PD-1/PD-L1) accelerate immune cell senescence. This bidirectional crosstalk establishes a complex regulatory network that facilitates immune evasion and drives resistance to immunotherapy. Targeting immune senescence and SASP-related signaling pathways presents a compelling strategy for reversing therapeutic resistance. As highlighted in this review, a diverse array of agents—including metformin, ABT-263, other senolytics, SASP inhibitors, and nanotechnology-based drug delivery platforms—have demonstrated potential in preclinical models to eliminate senescent cells, restore immune competence, and reprogram the TME. Among these, nanodelivery systems offer unique advantages in drug stability, specificity, and controlled release, expanding the landscape of combination strategies. The integration of senescence-targeted therapeutics with established immunotherapies—such as ICIs and CAR-T cells—represents a promising direction for next-generation precision oncology.

Despite considerable progress in elucidating the interplay between immune senescence and the TME, a major challenge remains: the absence of robust, specific, and sensitive biomarkers to accurately monitor immune senescence and immune suppression within the TME. Emerging high-dimensional technologies such as single-cell RNA sequencing, multiplex imaging, and spatial profiling provide exciting opportunities to address this gap. Advanced spatially resolved tools—including tissue-based cyclic immunofluorescence, imaging mass cytometry, and CODEX—enable detailed analysis of the spatial distribution and heterogeneity of senescent immune cells across different tumor types and patient populations (232–234). These platforms are instrumental in characterizing cellular interactions within the TME and guiding precision immunotherapeutic interventions. Notably, recent single-cell transcriptomic studies incorporating TCR sequencing have identified Granzyme K⁺ CD8⁺ T cells as a conserved marker of inflammatory senescence, whose prevalence increases with age (235, 236). Integrative multi-omics approaches combining flow cytometry, single-cell transcriptomics, and epigenetic clocks offer powerful means to identify and validate novel biomarkers. These biomarkers are critical for predicting immunotherapy response, selecting patients likely to benefit, and enabling real-time monitoring of treatment efficacy.

In summary, this evolving understanding of immune cell senescence and its reciprocal interaction with the TME paves the way for personalized, precision-guided cancer immunotherapy. By assessing immune senescence status, TME characteristics, and tumor mutational burden, clinicians can refine patient stratification and optimize the timing and composition of immunotherapeutic regimens. Looking ahead, the incorporation of validated biomarkers, widespread application of single-cell technologies, artificial intelligence-driven predictive modeling, and innovations in senolytic and nanomedicine platforms hold the potential to elevate the efficacy, safety, and personalization of cancer immunotherapy. These advances offer new hope for

improving clinical outcomes and quality of life for patients facing cancer.

Author contributions

DG: Writing – original draft, Writing – review & editing. PK: Writing – review & editing, Writing – original draft. YH: Conceptualization, Validation, Writing – review & editing. SS: Supervision, Writing – review & editing, Conceptualization. LT: Conceptualization, Writing – review & editing. FY: Funding acquisition, Supervision, Conceptualization, Writing – review & editing.

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Glossary

ACT	Adoptive Cell Therapy	ITIM	Tyrosine-based inhibition motif
AKT	Protein kinase B	JAK2	Janus kinase 2
APCs	Antigen-presenting cells	KLRG-1	Killer cell lectin-like receptor G1
Bcl-2	B-cell lymphoma-2	LAG-3	Lymphocyte Activation Gene-3
BFAR	Bifunctional apoptosis regulator	MAPK	Mitogen-activated protein kinase
Btk	Bruton's tyrosine kinase	MCP-1	Monocyte chemoattractant protein-1
cAMP	Cyclic AMP	MDSCs	Myeloid-derived suppressor cells
CAFs	Cancer-associated fibroblasts	MHC	Major histocompatibility complex
CAR	Chimeric antigen receptor	MMPs	Matrix metalloproteinases
CAR-T	Chimeric antigen receptor T cell	mTORC	Mammalian target of rapamycin complex
CCL	Chemokine (C-C motif) ligand	NK	Natural killer
CCR5	C-C chemokine receptor type 5	NKRs	Natural killer receptors
CEACAM1	Cell adhesion molecule 1	NSCLC	Non-small cell lung cancer
cDCs	Classical dendritic cells	PD-1	Programmed cell death protein 1
CODEX	CO-Detection by indEXing	PD-L1	Programmed death-ligand 1
CSC	Cancer stem cell	PI3K	Phosphatidylinositol-3-kinase
CTLA-4	Cytotoxic T lymphocyte-associated protein 4	PLGA	Poly(lactic-co-glycolic acid)
CXCL6	C-X-C motif chemokine ligand 6	PLL	Poly-L-lysine
DCs	Dendritic cells	PtdSer	Phosphatidylserine
ECM	Extracellular matrix	REP	Rapid expansion protocol
EGFR	Epidermal growth factor receptor	ROS	Reactive oxygen species
EGFR-19 del	EGFR exon 19 deletion	SASP	Senescence-associated secretory phenotype
EMT	Epithelial-mesenchymal transition	SH2	Src homology 2
ER	Endoplasmic reticulum	SOAT2	Sterol O-acyltransferase 2
GAC	Gastric adenocarcinoma	STAT1/3	Signal transducer and activator of transcription 1/3
GBM	Glioblastoma multiforme	TCR	T cell receptor
HER2	Human epidermal growth factor receptor 2	TCR-T	T cell receptor-engineered T cell
HLA	Human leukocyte antigen	TEXs	Exhausted T cells
HMGB1	High mobility group box 1	TIGIT	T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains
ICOS	Inducible T cell co-stimulator	TIL	Tumor-infiltrating lymphocytes
ICIs	Immune checkpoint inhibitors	TIM-3	T cell immunoglobulin and mucin domain-3
IDO	Indoleamine 2,3-dioxygenase	TME	Tumor microenvironment
IFN	Interferon	Tregs	Regulatory T cells
IL	Interleukin	uPAR	Urokinase-type plasminogen activator receptor
iNOS	Inducible nitric oxide synthase	ZAP-70	Zeta-chain-associated protein kinase 70.
irAEs	Immune-related adverse events		