Targeting the Senescent Tumor Microenvironment to Sensitize Immunotherapy

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Abstract. The tumor microenvironment (TME) plays a pivotal role in cancer progression, metastasis, and therapeutic resistance. Cellular senescence within the TME, characterized by irreversible growth arrest and the senescence-associated secretory phenotype (SASP), profoundly impacts tumor biology and immunotherapy efficacy. The senescent TME promotes tumor growth, invasion, and metastasis through complex interactions between senescent cells, SASP factors, and the extracellular matrix (ECM). Simultaneously, senescence-induced alterations in immune cell function, including T cell exhaustion, macrophage polarization, and impaired natural killer (NK) cell cytotoxicity, contribute to an immunosuppressive niche that hinders immunosurveillance and fosters tumor immune evasion. Mounting evidence suggests that the senescent TME is a critical mediator of resistance to immune checkpoint inhibitors (ICIs). Senescence-associated changes in the TME dampen antitumor immunity by reducing CD8+ T cell infiltration and functionality while promoting the accumulation of immunosuppressive cell populations such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Consequently, strategies targeting the senescent TME have emerged as promising approaches to enhance ICI efficacy. Senolytic agents, SASP inhibitors, and combinatorial therapies aimed at eliminating senescent cells, modulating SASP, and reprogramming the immunosuppressive TME have shown potential in preclinical models to sensitize tumors to immunotherapy. As our understanding of the senescent TME evolves, it is becoming increasingly clear that a multifaceted approach integrating TME-targeted interventions with immunotherapy is necessary to overcome resistance and improve patient outcomes. Future research should focus on elucidating the molecular mechanisms underlying senescence-driven immunotherapy resistance, identifying robust biomarkers to predict treatment response, and developing novel therapeutic strategies that synergize with ICIs. By harnessing the potential of TME-targeted approaches, we can expand the scope and efficacy of cancer immunotherapy, ultimately leading to improved survival and quality of life for cancer patients.

Keywords: Tumor Microenvironment, Cellular Senescence, Immunotherapy Resistance.

1. Introduction

ICIs augment antitumor immunity by blocking inhibitory pathways, such as cytotoxic t-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1/ programmed death-Ligand 1 (PD-1/PD-L1), which suppress T - cell activation. After the 2015 landmark U.S. Food and Drug Administration (FDA) approval of pembrolizumab for advanced melanoma [1], ICIs have revolutionized cancer management. Nevertheless, durable responses are observed in less than 30% of patients, and intrinsic and acquired resistance remain significant clinical challenges [2]. Improving immunotherapeutic efficacy necessitates a deeper understanding of TME modulation.

The TME is a dynamic ecosystem. Malignant cells interact with endothelial cells (ECs), fibroblasts, immune infiltrates, ECM, and signaling molecules, driving tumor proliferation, metastasis, and therapeutic resistance [3]. Hypoxia in the TME promotes aerobic glycolysis (Warburg effect), generating lactate that stabilizes hypoxia - inducible factor 1α (HIF - 1α). HIF - 1α upregulates carbonic anhydrase IX (CAIX), facilitating extracellular acidification, ECM degradation, and epithelial - mesenchymal transition, thereby enhancing tumor invasiveness [4]. Tumor cells also undermine immunity through nutrient competition, secretion of immunosuppressive metabolites (e.g., kynurenine), and metabolic reprogramming of T cells, creating an immune - evasive niche [5]. Notably, gut microbiota - derived trimethylamine N - oxide (TMAO) enhances type I interferon

signaling in pancreatic ductal adenocarcinoma [6], suggesting that microbial modulation could serve as an immunotherapeutic adjuvant. Emerging evidence emphasizes neutrophil plasticity in the TME. Engineered neutrophil extracellular vesicles delivering carfilzomib-loaded nanoparticles can significantly reduce circulating tumor cells and inhibit pre-metastatic niche formation via proteasome inhibition - mediated cytotoxicity [7].

Cellular senescence induces substantial TME alterations, known as the senescent TME. This is characterized by SASP, stromal cell aging, ECM remodeling, and immune dysregulation [8]. The senescent TME promotes tumor progression and confers resistance to conventional therapies and ICIs [9], for example, by enhancing PD - L1 expression and causing T - cell exhaustion. Although preclinical studies suggest the role of the senescent TME in immunotherapy failure, translational understanding remains limited. This review systematically analyzes current knowledge of senescent TME biology and its implications for immunotherapy, and proposes novel strategies to overcome microenvironment - driven treatment resistance. Elucidating these mechanisms may enable combinatorial approaches to expand the efficacy of ICIs across various malignancies.

2. The Impact of the Senescent Microenvironment on Tumors

2.1. Characteristics of the Senescent Microenvironment

The senescent TME is characterized by three key components: senescent cells, the SASP, and ECM remodeling. Senescent cells exhibit three hallmarks: irreversible cell cycle arrest, acquisition of SASP, and resistance to apoptotic cell death. Irreversible growth arrest, a cardinal feature of cellular senescence, is induced by telomere attrition, DNA damage, or oxidative stress. Unlike transient cell cycle arrest, senescent cells are permanently arrested in the G1/S phase despite maintaining metabolic activity. This state is associated with persistent upregulation of cell cycle regulators (e.g., cyclin-dependent kinase inhibitor 1A (p21), p16INK4a) and evasion of programmed cell death through mechanisms such as B-cell lymphoma 2 (Bcl-2) family protein upregulation, enabling their prolonged accumulation within tissues and exerting sustained paracrine effects.

SASP refers to the robust secretion of pro-inflammatory cytokines IL-6, IL-8, IL-10, chemokines, growth factors, and matrix metalloproteinases (MMPs) by senescent cells [9]. This secretory program mediates both beneficial immunosurveillance (e.g., clearance of damaged cells) and deleterious effects (e.g., chronic inflammation, tumor progression). For example, IL-6 exhibits context-dependent dual roles: while elevated IL-6 levels correlate with hepatocellular carcinoma (HCC) progression [10], IL-6 deficiency exacerbates liver carcinogenesis in murine models [11]. Similarly, galectin-9 demonstrates paradoxical effects, promoting immunosuppression in some contexts [12], while inhibiting melanoma metastasis in others [13]. In HCC, SASP derived from senescent hepatocytes reprograms tumor-associated macrophages (TAMs) to promote tumorigenesis [14], while SASP components like fimbrin-like protein 1 enhance HCC cell proliferation and motility [15]. SASP also recruits CCR2+ immature myeloid cells (iMCs) that suppress NK cell cytotoxicity [9].

ECM remodeling in the senescent TME involves structural degradation and increased stiffness [16]. For instance, collagen aging generates tumor-associated collagen signatures (TACS) that promote tumor invasion [17]. ECM rigidity modulates immune cell function: while increased stiffness impairs T cell infiltration, it enhances T Cell Receptor (TCR) engagement, T cell proliferation, and pro-inflammatory cytokine production [18]. Inflammatory mechanical stress from stiff matrices further induces T cell apoptosis [19]. Concomitant upregulation of MMPs degrades ECM barriers, altering chemokine gradients and facilitating tumor cell dissemination [20]. Collectively, these ECM alterations create a permissive niche for tumor progression while impeding immunosurveillance.

2.2. The Impact of the Senescent Microenvironment on Tumor Biology

2.2.1. Mechanisms by Which the Senescent Microenvironment Promotes Tumor Cell Proliferation

The senescent TME mediates profound impacts on oncogenesis through alterations in stromal components and secretory profiles. Senescence-associated changes within the TME influence tumorigenesis by modulating proliferation, invasion, metastasis, and angiogenesis [21]. STK40 has been identified as a critical aging-related gene driving gastric carcinogenesis, with in vitro studies demonstrating that STK40 ablation increases reactive oxygen species accumulation and impairs cancer cell proliferation [22]. Immune and stromal cells contribute to tumor growth via cytokine secretion: neutrophils exhibiting senescence-like phenotypes in the TME express the triggering receptor expressed on myeloid cells 2 (TREM2), a receptor mediating immunosuppression and tumorigenic promotion [23]. Senescent cancer-associated fibroblasts (CAFs) facilitate epithelial tumor cell expansion through transforming growth factor-beta 1 (TGFβ1) and stromal cell-derived factor-1 (SDF-1) secretion, enhancing proliferation, motility, and metastatic potential. These cells also upregulate ECM proteins, MMPs, and osteopontin, activating mitogen-activated protein kinase (MAPK) signaling to promote tumorigenic progenitor expansion [24]. Senescent cells further drive tumor growth through the SASP. SASP-derived IL-6 and IL-8 establish chronic inflammation within the TME, induce epithelial-mesenchymal transition (EMT), and recruit MDSCs [25]. MDSCs in turn suppress CD8+ T cell cytotoxicity, creating an immunosuppressive niche that protects tumor cells from immunosurveillance [26]. IL-6 specifically mediates MDSC recruitment, thereby enabling tumor progression while concurrently shielding malignant cells from senescence induction [27]. Collectively, these mechanisms highlight the multifaceted role of the senescent TME in fostering tumorigenesis through both direct cellular interactions and paracrine signaling networks.

2.2.2. The Impact of the Senescent Microenvironment on Tumor Cell Invasion and Metastasis

The senescent TME not only promotes tumor growth but also facilitates metastasis through multiple mechanistic pathways. Paracrine senescence of CAFs within the aging TME leads to their accumulation in tumor tissues, where they secrete prometastatic factors [28]. For example, gallbladder cancer (GBC) establishes an immunosuppressive TME populated by TAMs, Tregs, exhausted CD8+ T cells, and STMN1+ fibroblasts that drive tumor progression. FN1+TGM2+ fibroblast clusters preferentially localized to metastatic niches secrete SASP factors that enhance GBC cell motility [29]. CAFs further promote metastasis by altering ECM mechanics: lysyl oxidase (LOX) family enzymes disrupt de novo ECM deposition, increasing crosslinking and stiffness. This biomechanical remodeling promotes tumor cell invasion and treatment resistance by releasing sequestered growth factors and creating a permissive metastatic niche [30].

Beyond CAFs, SASP derived from diverse cell types contributes to metastatic dissemination. Senescence-induced IL-1α triggers downstream production of IL-6 and IL-8, establishing an inflammatory milieu that promotes tumorigenesis [31]. These cytokines also polarize macrophages toward an M2-like immunosuppressive phenotype, exacerbating TME dysfunction [32]. Collectively, these processes highlight the senescent TME as a critical mediator of metastatic progression through stromal reprogramming, ECM remodeling, and inflammatory signaling networks.

2.2.3. The Impact of the Senescent Microenvironment on Angiogenesis

The senescent TME influences tumor biology through modulation of angiogenesis, a critical process for neoplastic progression. Tumor vasculature exhibits structural and functional abnormalities distinct from normal tissues, with vascular ECs playing a central role in angiogenic sprouting and TME remodeling [33]. Senescent cells within the TME secrete pro-angiogenic factors including vascular endothelial growth factor, platelet - derived growth factor and fibroblast growth factor (VEGF, PDGF, and FGF), which induce endothelial activation and vascular remodeling [34]. Mikula-Pietrasik et al. demonstrated that senescent human peritoneal mesothelial cells enhance ovarian cancer cell secretion of CXCL1, CXCL8, HGF, and VEGF, thereby augmenting EC

angiogenic capacity [35]. Similarly, HCC tumors utilize SASP components such as IL-6, IL-8, CXCL10, and AREG to promote neovascularization [36]. Collectively, these findings highlight the senescent TME as a key regulator of tumor angiogenesis through paracrine signaling networks and endothelial reprogramming.

2.2.4. The Impact of the Senescent Microenvironment on Tumor Heterogeneity

The senescent TME contributes to tumor heterogeneity, a hallmark of malignancy with critical implications for treatment response and progression. Tumor heterogeneity encompasses three distinct dimensions: intratumoral, intertumor , and microenvironmental. Intratumoral heterogeneity arises from clonal evolution driven by genetic mutations, epigenetic reprogramming, and microenvironmental selection pressures [37]. Senescent cancer cells exhibit distinct interaction patterns with stromal components compared to non-senescent counterparts: non-senescent cells preferentially engage ECs to facilitate metastasis, while senescent cells demonstrate reduced PD-L1 engagement with T cells [38]. This differential crosstalk propagates spatial heterogeneity in TME aging markers, with stromal cells (fibroblasts, ECs) displaying more pronounced senescence compared to malignant cells. Among immune subsets, myeloid cells exhibit higher senescence burden than T lymphocytes [38].

HCC exemplifies this complexity, arising in cirrhotic livers characterized by chronic inflammation, fibrosis, and regenerative nodules. This pre-neoplastic milieu promotes profound inter- and intratumoral heterogeneity through interactions between senescent hepatocytes, activated stellate cells, and inflammatory infiltrates [39]. SASP factors released by these cells create spatiotemporally variable inflammatory niches that drive clonal selection and phenotypic diversification. Collectively, the senescent TME acts as both a consequence and driver of tumor heterogeneity, perpetuating adaptive evolution through dynamic stromal-epithelial interactions and immunosuppressive signaling networks.

3. Alterations In Immune Cell Function Induced By The Senescent Microenvironment

3.1. Changes in T Cell Function

The senescent TME induces pleiotropic effects on T cell biology, characterized by numerical declines, phenotypic shifts, and functional impairments. Senescent tumors demonstrate preferential recruitment of CD4+ T cells, CD8+ T cells, and CD11b+ myeloid cells [8], accompanied by reduced frequencies of memory and effector subsets within CD4+ and CD8+ compartments [40]. Naive T cell proportions decrease significantly [41], with CD28+ T cells comprising only 10–15% of CD4+ and 50–60% of CD8+ populations [40]. CD4+ T cell dysfunction manifests as defective activation, interleukin-2 production, and B cell help [42], compounded by skewed differentiation toward activated regulatory T cells (aTregs), exhausted T cells, and cytotoxic subsets (collectively ~30% of CD4+ T cells) [41]. Age-related disruptions in naive-to-memory T cell ratios further compromise immunosurveillance [43].

CD8+ T cells exhibit heightened susceptibility to immunophenotypic and functional alterations during aging, attributed in part to mitochondrial dysfunction [44]. Senescent prostate cancer cells secrete IL-6, CXCL1, and CXCL2, which suppress CD8+ T cell cytotoxicity and promote tumorigenesis [44]. Subset analysis reveals declines in GZMK+ and GZMB+ CD8+ T cell populations [45], coinciding with reduced proliferation, effector function, and upregulation of inhibitory receptors (PD-1, TIM-3, CTLA-4, LAG-3) [46]. Senescent CD8+ T cells uniquely overexpress TIGIT (an ITIM-domain-containing receptor) [47] and CD38 (a NAD+ hydrolase) [48], while TLR4 upregulation occurs in aged murine models [49]. Treg dynamics are also perturbed in the senescent TME, with Foxp3+ CD4+ Treg frequencies increasing alongside CD25+ Tregs and CD8+ Tregs [40]. Single-sample gene set enrichment analysis (ssGSEA) demonstrates positive correlations between aging scores and immunosuppressive cell populations (induced Tregs [iTregs],

central memory T cells [Tcms], natural Tregs [nTregs]), while inversely correlating with effector cell subsets like NK cells [50]. Collectively, these alterations create an immunosuppressive niche characterized by T cell replicative senescence, receptor dysregulation, and skewed subset distributions, fostering tumor immune evasion and therapeutic resistance.

3.2. Changes in macrophage function

Senescent TME impairs macrophage effector functions [51], particularly phagocytosis. In murine models, cellular senescence reduces peritoneal macrophage and microglial phagocytic capacity [52]. Phenotypically, senescent macrophages exhibit increased CD73 and CD39 expression, attributed to IL-6 secreted by senescent tumor cells activating the JAK/STAT3 pathway [8]. This drives macrophage polarization toward a stable M2-like phenotype [53]. PTEN-deficient senescent tumors activate JAK2/STAT3 signaling, inducing CXCL1, CXCL2, and IL-6 secretion to promote M2 macrophage differentiation. While specific chemokines/cytokines vary across cancer types, senescent cells universally orchestrate macrophage reprogramming via paracrine signaling [34].

Senescent cells further modulate macrophage activation by secreting SASP factors that trigger NF-κB-dependent inflammation [14], recruiting macrophages and propagating paracrine senescence [54]. Senescent macrophages themselves secrete IL-1α, IL-6, and IL-8, which recruit immunosuppressive Tregs and NK cells to the TME [55]. In glioblastoma, senescence-induced M2-polarized TAMs secrete IL-1β, which promotes tumor growth via STAT3/NF-κB signaling while fostering a pro-inflammatory TME permissive for malignant progression [56]. Collectively, these alterations highlight the senescent microenvironment as a critical regulator of macrophage dysfunction, immunosuppression, and tumorigenesis.

3.3. Decline in NK cell activity

SASP factors within the aging microenvironment exert dual effects on NK cell recruitment and function. In early-stage tumors, senescent HCC cells secrete SASP components including CCL2, IL-15, and CXCL1, which chemoattract macrophages, neutrophils, and NK cells to facilitate immunosurveillance and tumor growth inhibition. However, in advanced disease, SASP-derived CCL2 paradoxically suppresses NK cytotoxicity, creating an immunosuppressive niche [34]. This functional dichotomy highlights context-dependent roles for senescence-associated chemokines in tumor progression.

NK cells, defined by $CD3^{-}CD16^{+}CD56^{+}$ expression, exhibit senescent-related phenotypic shifts: CD56dim NK cells increase significantly in circulation, while CD56bright NK cell frequencies decline precipitously. These changes correlate with reduced cytolytic capacity and interferon-γ production, impairing immunosurveillance against senescent tumor cells [57]. Collectively, the aging microenvironment disrupts NK cell homeostasis through chemokine-mediated recruitment and subset dysregulation, contributing to tumor immune evasion.

3.4. Changes in B cell and Dendritic cell (DC) function

Senescent TME induces significant alterations in B cell homeostasis, characterized by reduced naive B cell frequencies and expanded memory B cell populations, coinciding with decreased antibody affinity for antigens. The transcription factor Miz-1 plays a critical role in early B cell development, regulating both germinal center responses and memory B cell differentiation. Miz-1-deficient mice exhibit profound reductions in bone marrow B cell and pre-B cell numbers [58].

Senescent cells promote DC recruitment and activation while maintaining antigen-presentation capacity [59]. Senescent TME stiffening enhances inflammatory and phagocytic capacities of bone marrow-derived DCs through increased IL-6 and TNF-α production. Mechanistically, ECM rigidity upregulates glycolytic metabolism in DCs, evidenced by elevated glycolytic gene expression, glucose uptake, and metabolic activity. Stress-induced glycolysis is critical for DC-mediated type I interferon responses and $CD8^{+}$ T cell priming [60]. In aged murine models, conventional DCs (cDCs) and monocyte-derived DCs (MoDCs) represent the primary antigen-presenting cell subsets driving

antitumor immunity [61]. Marin et al. demonstrated that vaccination with senescent cancer cells elicits robust antitumor protection dependent on DC activation and $CD8^+$ T cell responses [59]. Collectively, these findings highlight the dual role of the senescent TME in shaping DC functionality, balancing immunosurveillance with inflammatory dysfunction.

3.5. Impact on antigen presentation

The senescent TME impairs antigen presentation through multiple mechanisms, contributing to tumor immune evasion and therapeutic resistance. In anti-PD-1–non-responsive patients, β2M mutations in tumor cells abrogate major histocompatibility complex (MHC) class I surface expression, compromising antigen presentation capacity [62]. Senescent TME also dampens intratumoral $CD8^+$ T cell expansion, attenuating αPD-L1 immunotherapy efficacy [63]. Senescent $CD8^+$ T cells, particularly THEMIShi subsets [64], secrete pro-inflammatory cytokines (TNFα, IFNγ) and matrix-remodeling enzymes, fostering tumor progression while reducing ICI responsiveness [65]. Reduced IL-2 production in senescent $CD8^+$ T cells maintains Treg cell homeostasis, blunting antitumor immunity and further limiting ICI efficacy [66].

Beyond effector dysfunction, senescent T cells exhibit metabolic reprogramming and signaling/gene regulatory alterations, exacerbating functional impairments and resistance to immune checkpoint blockade [67]. Myeloid cells within the TME further suppress $CD8^+$ T cell activity via immunosuppressive mechanisms; preclinical studies demonstrate that myeloid cell depletion restores $CD8^+$ T cell proliferation and reverses immunotherapy resistance [63]. Collectively, these alterations highlight the senescent TME as a critical mediator of antigen presentation dysfunction, immunosuppression, and treatment failure.

4. Clinical translation: Senescent microenvironment and immunotherapy

Senescent TME profoundly impact immune cell generation and function, thereby shaping tumor behavior. In clinical settings, the senescent cellular milieu directly influences immunotherapy efficacy by modulating immune cell dynamics and tumor immunosensitivity. These senescent TME changes create a complex interplay between host immunity and malignant progression, underscoring the need for tailored therapeutic strategies targeting the senescent TME.

4.1. Reducing the efficacy of immunotherapy

Emerging evidence links immunotherapy resistance to the development of a senescent microenvironment. Recent investigations have interrogated the impact of cellular aging on ICI responsiveness. Maggiorani et al. demonstrated that senescent cell ablation in murine models restored myeloid cell functionality, improving overall survival and ICI efficacy [63]. Specifically, targeting $p16^+$ senescent cells via the p16-3MR system with ganciclovir (GCV) rescued αPD-L1 therapy responsiveness. Subsequent studies revealed that stromal cell senescence within tumors reduces αPD-L1 efficacy [63], while a 14-gene SASP signature in cancer cells correlates with poor outcomes in non-small cell lung cancer (NSCLC) patients treated with ICIs. NSCLC patients with high SASP signature expression exhibit shorter progression-free survival and 1-year overall survival [68]. Mouse models further show that treatment-induced senescence (TIS) impairs αPD-L1 efficacy by reducing intratumoral $CD8^+$ T cell frequency and activity [63]. In NSCLC patients undergoing PD-1/PD-L1 monotherapy, $CD28^-CD57^+KLRG1^+CD8^+$ T cell enrichment—a hallmark of immunosenescence—correlates with ICI resistance. Patients exceeding 39.5% $CD28^-CD57^+KLRG1^+$ cells in $CD8^+$ T cell populations demonstrate zero response rates, with significantly shorter progression-free and overall survival [66].

Sensitive and specific biomarkers are critical for clinical prediction, with microenvironmental aging-related markers serving as key indicators. The EC.SENESCENCE.sig, a thymic epithelial cell senescence signature, predicts survival and immunotherapy response across malignancies. This signature inversely correlates with tumor mutation burden (TMB) in breast (BRCA), head and neck

(HNSC), and cervical (CESC) cancers, enhancing its utility as a predictive tool (AUC 0.66–0.79) [69]. Biao Gao et al. developed the CS score, integrating immune checkpoint molecule levels to predict outcomes in Hepatitis B virus (HBV)-related liver cancer patients undergoing ICIs [70]. Wang et al. stratified esophageal cancer (ECa) patients into high- and low-risk groups based on a senescence-related gene expression signature, with Tumor Immune Dysfunction and Exclusion (TIDE) algorithm analysis identifying high-risk patients as prone to treatment resistance and low-risk patients as deriving greater benefit from immunotherapy [71]. Collectively, these findings highlight the senescent microenvironment as a critical determinant of ICI efficacy and underscore the need for aging-targeted biomarkers in precision oncology.

4.2. Targeting the TME to sensitize immunotherapy

Reversing tumor-infiltrating T cell senescence enhances antitumor immunity and improves immunotherapy outcomes. Strategies include blocking ATM-dependent DNA damage responses and MAPKp38 signaling in tumor-specific T cells, which restored anti-PD-L1 checkpoint blockade efficacy in B16 melanoma models [72]. Glycolysis restriction in melanoma similarly attenuates T cell senescence and potentiates checkpoint therapy [73]. Senolytic agents, such as ABT-263/ABT-737 (BCL-2 family inhibitors) and dasatinib-quercetin combinations, eliminate senescent cells by targeting anti-apoptotic pathways[30, 74]. In murine models, ABT263 augmented αPD-L1 efficacy in tumors arising in irradiated aged mice (6.5 Gy TBI) [63]. Advanced senolytics include lysosome- and SA-β-galactosidase-activated prodrugs/nanoparticles, as well as Na^+/K^+-ATPase-dependent cytotoxins [75]. Daniel Muñoz-Espín et al. developed galactoside-conjugated cytotoxins exploiting senescent cell lysosomal β-galactosidase activity [76]. Chimeric antigen receptor (CAR) T cells targeting urokinase-type plasminogen activator receptor (uPAR) also effectively eliminate senescent cells [77]. Inhibiting anti-apoptotic genes like MCL-1 with S63845 induces senescence and enhances ICI responsiveness in prostate cancer [78]. ECM remodeling via ABT737-mediated senescent CAF ablation slows tumor growth in the murine mammary tumor virus polyomavirus middle T antigen mouse model (MMTV-PyMT) mice and improves ICIs [79].

SASP inhibition represents a critical therapeutic axis. Current SASP inhibitors target signaling pathways (TAK1, p38MAPK, mTOR, NF-κB, JAK2/STAT3) to suppress SASP secretion [30]. Rapamycin blocks IL1A production, inhibiting senescent fibroblast-mediated tumorigenesis [80], while metformin suppresses NF-κB nuclear translocation by inhibiting IκB phosphorylation [81]. Flavonoids like apigenin and kaempferol modulate senescent cell behavior and enhance ICI efficacy [82]. Combinatorial approaches, such as Ali + JAK2 inhibitor ruxolitinib (Rux) or APR-246 + pembrolizumab, reprogram SASP to reduce M2 macrophage polarization and promote p53-dependent T cell expansion [83, 84]. Antibody-based targeting of SASP components (IL-6, PGE2, IL-1β, TGF-β) depletes immunosuppressive MDSCs, sensitizing tumors to anti-PD-1 therapy [85]. Collectively, these strategies highlight the potential of TME-targeted interventions to overcome senescence-driven immunotherapy resistance.

5. Summary and Perspective

A series of changes can occur in the TME, including cellular senescence, SASP, and ECM remodeling. This resulting senescent TME not only promotes tumor progression and metastasis, but also leads to resistance of tumors to various anti-tumor treatments. Specifically, the senescent TME affects the efficacy of ICIs through various mechanisms: First, The senescent TME causes declines in the number and function of T cells, including CD4+ T cells, CD8+ T cells, and Treg cells, thereby weakening the anti-tumor immune response. The senescent TME also polarizes macrophages into the M2 type, promoting tumor growth. Meanwhile, the secreted cytokines inhibit the activities of NK cells and DCs. Lastly, SASP refers to proinflammatory factors and proteases secreted by senescent cells that can inhibit immune responses by recruiting immunosuppressive cells.

In summary, the senescent TME weakens anti-tumor immune surveillance and response by altering immune cell number and function, thus reducing immune checkpoint inhibitor efficacy. Identifying biomarkers of the senescent TME may help predict immunotherapy responses. Interventions targeting the senescent TME could potentially increase patient sensitivity to ICIs.

Although the relationship between the senescent TME and immunotherapy response is recognized, specific mechanisms need further elucidation. Future research may focus on:

Exploring molecular mechanisms by which the senescent TME affects different immune cells, providing a basis for targeted interventions.

Developing biomarkers related to the senescent TME and models to evaluate immunotherapy responses to achieve personalized medicine.

Developing drugs directly targeting the senescent TME, such as senolytics and SASP pathway inhibitors, to increase patient sensitivity to ICIs.

Investigating relationships between the senescent TME, tumor heterogeneity, and immune evasion to find new ways to reverse tumor immune escape.

Designing clinical trials evaluating therapies directly targeting the senescent TME with ICIs.

In summary, investigating the senescent TME and tumor immune tolerance, along with developing novel therapies, is expected to expand the population benefiting from ICIs and improve cancer patient outcomes.

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