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Immunosenescence promotes cancer development: from mechanisms to treatment strategies

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Abstract

The body's innate immune system plays a pivotal role in identifying and eliminating cancer cells. However, as the immune system ages, its functionality can deteriorate, becoming dysfunctional, inefficient, or even inactive—a condition referred to as immunosenescence. This decline significantly increases the risk of malignancies. While the pro-cancer effects of T-cell aging have been widely explored, there remains a notable gap in the literature regarding the impact of aging on innate immune cells, such as macrophages and neutrophils. This review seeks to address this gap, with emphasis on these cell types. Furthermore, although certain cancer immunotherapies, including immune checkpoint inhibitors (ICIs), have demonstrated efficacy across a broad spectrum of cancers, elderly patients are less likely to derive clinical benefit from these treatments. In some cases, they may even experience immune-related adverse events (irAEs). While senolytic strategies have shown promise in exerting anti-cancer effects, their adverse reactions and potential off-target effects present significant challenges. This review aims to elucidate the pro-cancer effects of immunosenescence, its implications for the efficacy and safety of ICIs, and potential anti-aging treatment strategies. In addition, optimizing anti-aging therapies to minimize adverse reactions and enhance therapeutic outcomes remains a critical focus for future research endeavors.

Highlights

- Senescence is an inevitable phenomenon in the human body, and scientists have explored the specific mechanisms by which immunosenescence advances the development of cancer.
- This review summarizes the mechanisms and characteristics of immunosenescence, which can be used as a level of surveillance for cancers due to immunosenescence.
- "Targeting immunosenescence" may be a new idea and strategy for cancer therapy.

Keywords Immunosenescence, Cancer, Senescence, Cancer therapy

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Introduction

With advancing age, the immune system also undergoes a natural aging, process known as immunosenescence [1]. This phenomenon results in immune dysfunction, reduced efficiency, or ineffectiveness, thereby elevating the risk of malignant tumor development [2]. In addition, immunosenescence can be influenced by various factors, including genetics, physical activity, nutrition, and infections such as human cytomegalovirus [3, 4]. A significant rise in the number of cancer patients is anticipated in the coming years, with approximately 60% of new cases and 70% of cancer-related deaths occurring in individuals aged 65 and above [5]. What is even more concerning is that immunosenescence can have a negative impact on cancer treatments such as ICIs. While ICIs have demonstrated considerable potential across various cancer types and are often employed as first-line therapies [6], their efficacy in elderly patients is often limited, with some experiencing irAEs. Targeting immunosenescence in cancer could potentially mitigate or even reverse tumor progression. Therefore, this review seeks to examine the role of immunosenescence in cancer development and treatment, with a focus on the effects of aging on immune function and the challenges of immunotherapy in older patients. Although senolytic therapies have shown promise in preventing immunosenescence and tumor progression to some extent, concerns regarding their safety and potential off-target effects remain significant barriers to their application in cancer therapy [7, 8]. Recent studies suggest that nanotechnology and chimeric antigen receptor (CAR)-T cell therapies may address these limitations, offering enhanced safety and efficacy. Thus, investigating safe and efficient strategies to target immunosenescence represents a critical area of exploration in the pursuit of effective cancer treatments.

Multiple mechanisms of immunosenescence

Aging is now understood to be the primary driver of immunosenescence, a universal and inevitable biological phenomenon characterized by the gradual loss and degradation of biological tissue structure and physiological functions [9]. Cellular senescence, a key aspect of this process, involves a stable and long-term arrest of the cell cycle, accompanied by morphological abnormalities and a loss of proliferative capacity [10, 11]. Proliferation arrest is one of the key characteristics of cellular senescence. The p53 protein plays a central role in mediating age-related proliferation arrest. Activation of p53, triggered by the DNA damage response (DDR) signaling cascade, results in cell cycle arrest [12, 13]. Downstream of p53, p21—a cyclin-dependent kinase inhibitor (CDKI)—inhibits CDK-cyclin complexes, causing the cell cycle to stall in the G1 phase and ultimately leading to cellular senescence [14]. Similarly, p16, another CDKI, disrupts the CDK4/6-cyclin D complex necessary for the G1-to-S phase transition, further negatively regulating the cell cycle [14]. The hypersecretory phenotype, referred to as senescence-associated secretory phenotypes (SASPs), is another key characteristic of cellular senescence [13]. However, the SASPs are not stable; instead, it is highly dynamic [15]. Indeed, senescence-associated phenotypes are temporal, and early-stage senescent cells are phenotypically different from late-stage senescent cells [16–18]. Induction of p21-driven SASPs is considered an early event [19], whereas upregulation of p16-driven SASPs is evident at later stages of senescence [20]. This temporal regulation of senescence-associated phenotypes seems to be controlled by the sequential and dynamic activation of diverse transcriptional programmes and hierarchies [16–18]. The ability of navitoclax and dasatinib and quercetin (D + Q) to selectively eliminate senescent cells has been tested *in vitro and in vivo* [21], and these agents markedly reduced SASP-driven signs of systemic inflammation [21–23]. This process of cellular senescence also occurs within the immune system, contributing to immunosenescence. As a result, the number, phenotype, and metabolic activity of immune cells undergo significant changes with age (Fig. 1). In addition, factors such as antigenic stimulation and thymus involution are widely acknowledged to influence the process of immunosenescence (Fig. 2). Besides, recent scientific discoveries have identified associations between immunosenescence and epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation [24]. However, the precise mechanisms underlying these associations remain to be fully elucidated and warrant further investigation.

Immunosenescence can lead to significant alterations in immune cells and impair immune responses, thereby contributing to the development of various diseases, including cancer and cardiovascular disorders. This process can be activated by multiple factors, such as persistent antigen stimulation, thymic involution, chronic inflammation, and damage to the telomere-telomerase system.

Antigenic stimulation

Current evidence suggests that antigenic stimulation is one of the primary drivers of immunosenescence [24, 25]. This antigenic stimulus can originate from various sources, including foreign viruses or endogenous cells. For instance, studies have shown that CD8 T cells from cytomegalovirus-infected patients often exhibit a CD28-CD57 + phenotype and undergo clonal expansion. This expansion leads to the depletion of the T-cell repertoire and, ultimately, the deterioration of T-cell-mediated immune functions [26]. In cancer patients, tumor-associated regulatory T cells (Tregs) within the

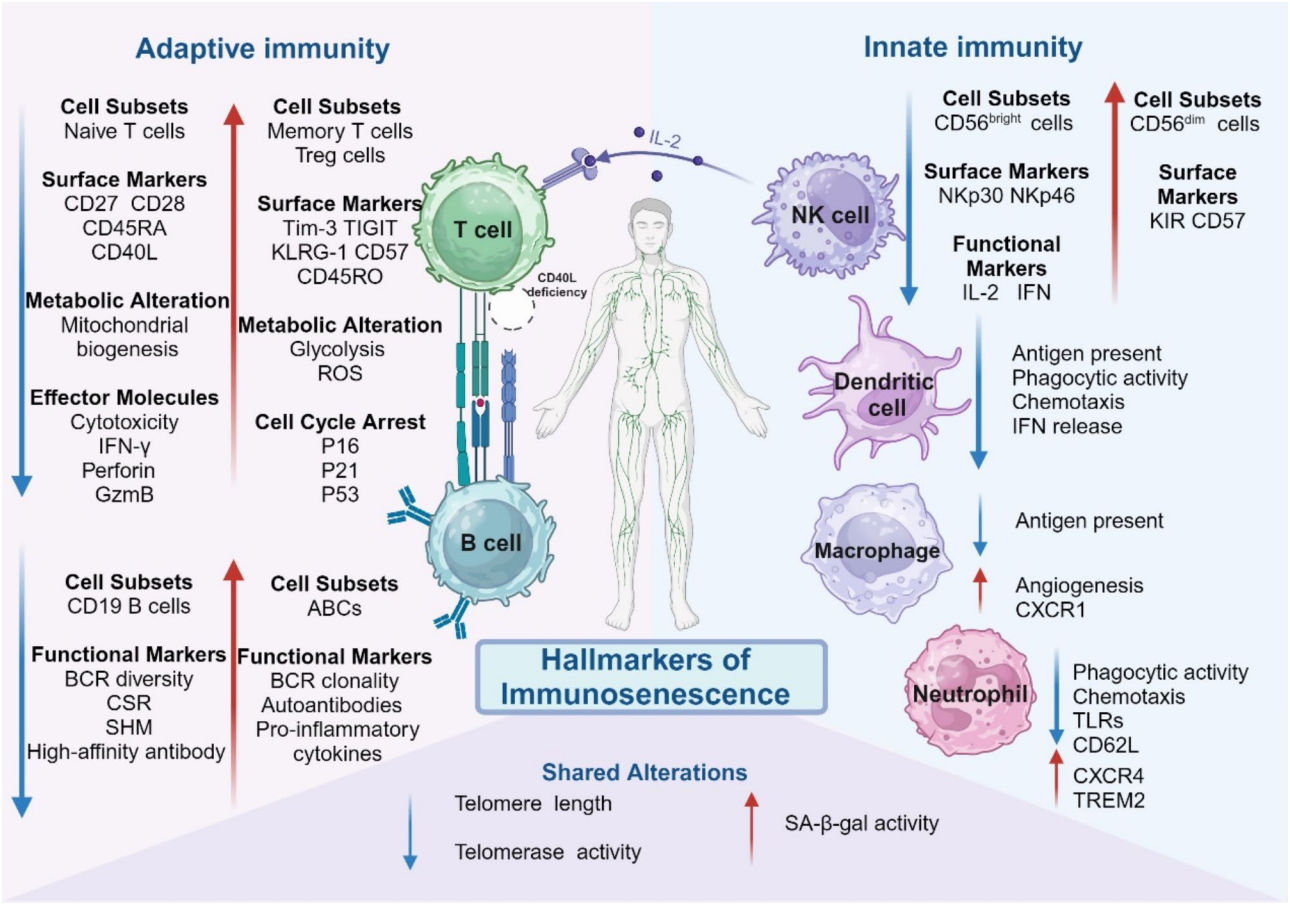

Fig. 1 Immune cell alterations related to immunosenescence. During immunosenescence, there are alterations in various cell subsets, surface markers, and other molecular markers of both innate immune cells (NK cells, DCs, macrophages, and neutrophils) and adaptive immune cells (T cells and B cells)

tumor microenvironment (TME) are frequently upregulated. Competition for glucose between Tregs and effector T cells activates ATM, triggering the extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 pathways. This activation, in turn, stimulates signal transducer and activator of transcription 1/3 (STAT1/3), leading to the upregulation of p16, p21, and p53. These molecular changes result in the termination of the T-cell cycle and the induction of cellular aging [27].

Thymus involution

With age-related thymic degeneration, the cortex-to-medulla ratio declines, along with a significant loss of thymocytes, leading to a reduced naïve T cell pool and a narrower T cell receptor (TCR) repertoire, particularly affecting CD8 + T cells [28]. In response, peripheral naïve T cells proliferate compensatorily to maintain T cell homeostasis, transitioning into memory T cells only upon antigenic stimulation [29]. Clinical studies have further corroborated these findings, showing a marked decrease in postoperative naïve T-cell production and a severe imbalance in the naïve-to-memory T cell ratio in patients who have undergone thymectomy [30, 31], providing clinical evidence that thymic degeneration is a key driver of immune system aging. Thea Newman's research team found that age-related thymus involution weakens T cell anti-tumor immunity. Analyzing data from 2 million cancer patients aged 18–70, they found that immunosenescence caused by thymus involution was highly correlated with the incidence rate of 57 cancer types [32].

Chronic inflammation

The chronic low-grade inflammatory response associated with advanced age is a key contributor to immunosenescence. Cellular senescence is central to the inflammaging process. As one of the key features of cellular senescence, SASPs secrete a plethora of soluble factors, including interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α), chemokines like IL-8 and CXCL-1, and extracellular matrix proteases [33], leading to the inflammaging phenotype. The persistent secretion of these SASPs suppresses immune cell function, further exacerbating immune decline [34]. Matthew D. Park's research team discovered age-related decline in DNA methyltransferase

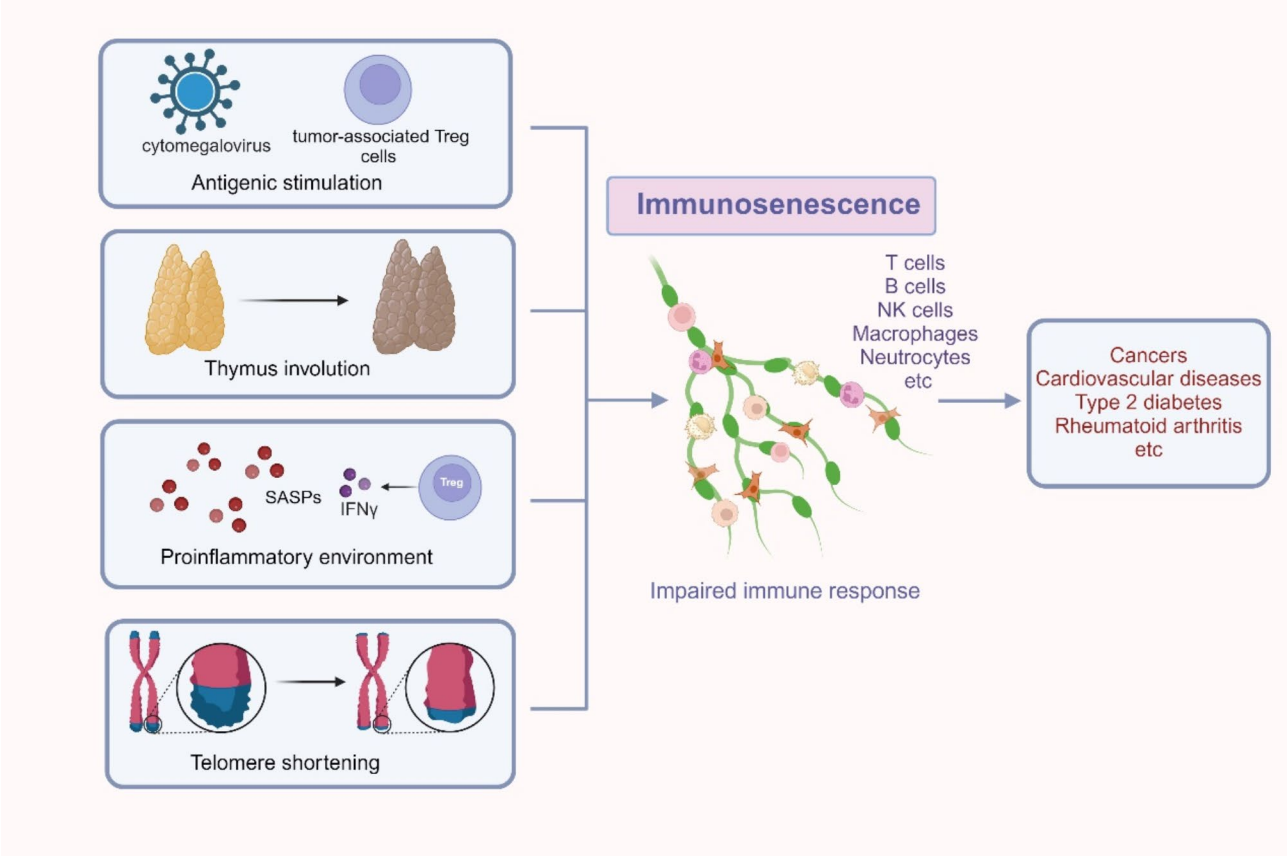

Fig. 2 Mechanisms of immunosenescence

3 A (DNMT3A) could boost IL-1α production, driving lung, colon, and pancreatic cancers in mice via the IL-1α/IL-1R1 axis. Anti-IL-1α antibodies slowed tumor growth by blocking this pathway. They also noted higher IL-1α mRNA levels in tumors from patients aged ≥ 70 compared to younger patients, highlighting its potential as a lung cancer risk predictor [35]. Moreover, this inflammatory response stimulates an increase in Tregs, which secrete transforming growth factor-β (TGF-β). TGF-β, in turn, suppresses the differentiation of helper T (Th) cells, reduces the cytotoxicity of CD8 + T cells and natural killer (NK) cells, and impairs the production of protective antibodies by B cells [36]. Recent scientific discoveries have revealed that the NF-κB-like immune deficiency (IMD) pathway plays a critical role in inducing inflammatory responses and contributing to immunosenescence. This process is regulated by the IMD receptor subtype, known as regulatory PGRP-LC (rPGRP-LC). Syntaxin 13 (Syx13) facilitates the formation of the endolysosomal system, which is responsible for the degradation of rPGRP-LC. The Target of Rapamycin Complex 1 (TORC1) - S6 kinase (S6K) signaling pathway downstream of rapamycin inhibits this mechanism, thereby promoting inflammatory responses and accelerating immunosenescence [37]. In addition, immunosenescence manifests more severely in female fruit flies compared to their male counterparts [37], suggesting the importance of considering gender as a factor in future studies on aging and immunosenescence.

Damage to the telomere-telomerase system

Cellular senescence is closely linked to the telomere-telomerase system. In lymphocytes, both mean telomere length and telomerase activity decline with age. Telomere shortening and reduction in telomerase activity contribute to DNA damage and cell cycle arrest, ultimately resulting in the functional decline of lymphocytes [38]. In a case-control study involving over 1,500 samples, Halcyon Skinner et al. found that age-related telomere shortening was associated with an increased prevalence of pancreatic cancer, with shorter telomeres increasing the risk. The study also associated telomere shortening with other cancer types, including colon cancer [39]. Consistently, another report confirmed that telomere shortening elevated the risk of leukemia and other malignant tumors [40].

Immunosenescence, driven by antigenic stimulation, thymic involution, chronic inflammation, and telomere damage, contributes to cancer development. While adaptive immune cell immunosenescence has

been well-studied [41], the impact of innate immune cell immunosenescence on cancer progression and immunotherapy—particularly in the context of ICIs—remains an area requiring further exploration. Besides, the development of targeted anti-aging strategies for specific cancer types represents a promising direction for future research.

Immunosenescence is a booster for cancer

Immunosenescence, triggered by various factors, leads to immune cell changes that significantly increase cancer risk. With the global elderly population projected to reach 22% by 2050, this trend underscores its growing impact [42]. Consequently, despite substantial advancements in overall life expectancy, the prevalence of age-related diseases continues to rise significantly. While the role of senescent adaptive immune cells in cancer progression has been extensively reviewed in other studies, the pro-cancer effects of senescent innate immune cells remain relatively underexplored. Therefore, this discussion focuses on the mechanisms through which senescent innate immune cells promote cancer development. Indeed, senescent immune cells undergo significant changes in quantity, phenotype, and metabolic function (Fig. 1). Research has demonstrated that immunosenescencent cells share several common characteristics. For instance, during aging, there is an increase in senescence-associated β-galactosidase (SA-β-gal) activity [43], as well as telomeres shortening and reduced telomerase activity in these cells [44]. Beyond these shared features, immunosenescent cells exhibit unique alterations specific to their type. Identifying these key changes is essential for advancing our understanding of tumor progression and improving prognostic evaluations.

Innate immune cells

NK cells

NK cells are a cornerstone of innate immunity, playing critical roles in immunoregulation and cytotoxicity. However, aging induces significant changes in the number, phenotype, and function of NK cells. In aged mice, NK cell counts across in all lymphoid organs are reportedly significantly reduced [45]. Among the two main subpopulations of NK cells, the immature $CD56^{bright}$ subset, known for its robust cytokine secretion capacity, is diminished in older individuals, while the mature CD56dim subset becomes more prevalent [46]. Research indicates that NK cells in the elderly secrete less interleukin-2 (IL-2) and interferon (IFN), a decline likely associated with the reduction in $CD56^{bright}$ NK cells. IL-2, a key mediator bridging innate and adaptive immunity, is essential for the proliferation of T cells and NK cells, and its decreased levels significantly impair immune responses [47]. Similarly, the antiviral, antitumor, and immunomodulatory effects of IFN are substantially weakened, contributing to an increased susceptibility to tumors in older adults. Furthermore, as the $CD56^{dim}$ NK cell population expands, there is an upregulation of Killer-cell Immunoglobulin-like Receptors (KIRs) and CD57, which are recognized markers of NK cell aging [48]. The cytotoxic capacity of NK cells is largely governed by their receptor expression; however, the proportion of NK cells expressing activating receptors such as NKp30 or NKp46 declines with age, potentially facilitating tumor cell evasion [49], consistent with research showing a significant reduction in cells expressing NKp30 or NKp46 in patients with pancreatic, gastric, and colorectal cancer [50].

Macrophages

In elderly individuals, the population of M2-like macrophages, which possess pro-angiogenic properties, is increased. Concurrently, the expression of co-receptors and major histocompatibility complex (MHC) class II molecules in macrophages is reduced, leading to a decline in their antigen-presenting capacity. These changes may collectively contribute to cancer development [51, 52]. Researchers have analyzed and compared cancerous tissues with normal tissues from a lung adenoma mouse model, revealing that senescent cells accumulate in lung adenocarcinoma lesions and promote the formation of lung adenomas. Further investigation identified these senescent cells as tissue-resident $CXCR1^{High}$ alveolar macrophages. The surface molecule $CXCR1^{High}$ serves as a marker of macrophage aging, and these cells were found to inhibits the ability of cytotoxic T cells (CTL) to kill cancer cells [53], thereby indirectly facilitating tumor progression. Besides, these senescent macrophages promote the release of SASP factors and induce angiogenesis, which supports tumor proliferation [54], directly contributing to tumor development [55] (Fig. 3). This phenomenon was further validated in a follow-up study, where the removal of senescent alveolar macrophages delayed the development of lung adenomas in mice. Importantly, tissue-resident $CXCR1^{High}$ alveolar macrophages were also detected in lung samples from patients with adenocarcinoma in situ (AIS), supporting the hypothesis that senescent alveolar macrophages play a role in the development of early-stage lung cancer [56]. However, several questions remain to be addressed. Firstly, are cancer cells involved in creating senescent alveolar macrophages? Secondly, how do specific SASP factors drive lung adenocarcinoma progression? Finally, do senescent macrophages also promote other cancers?

Neutrophils

Neutrophils play a critical role in innate immunity; however, in older adults, their function is compromised, with reduced phagocytic activity, impaired chemotaxis,

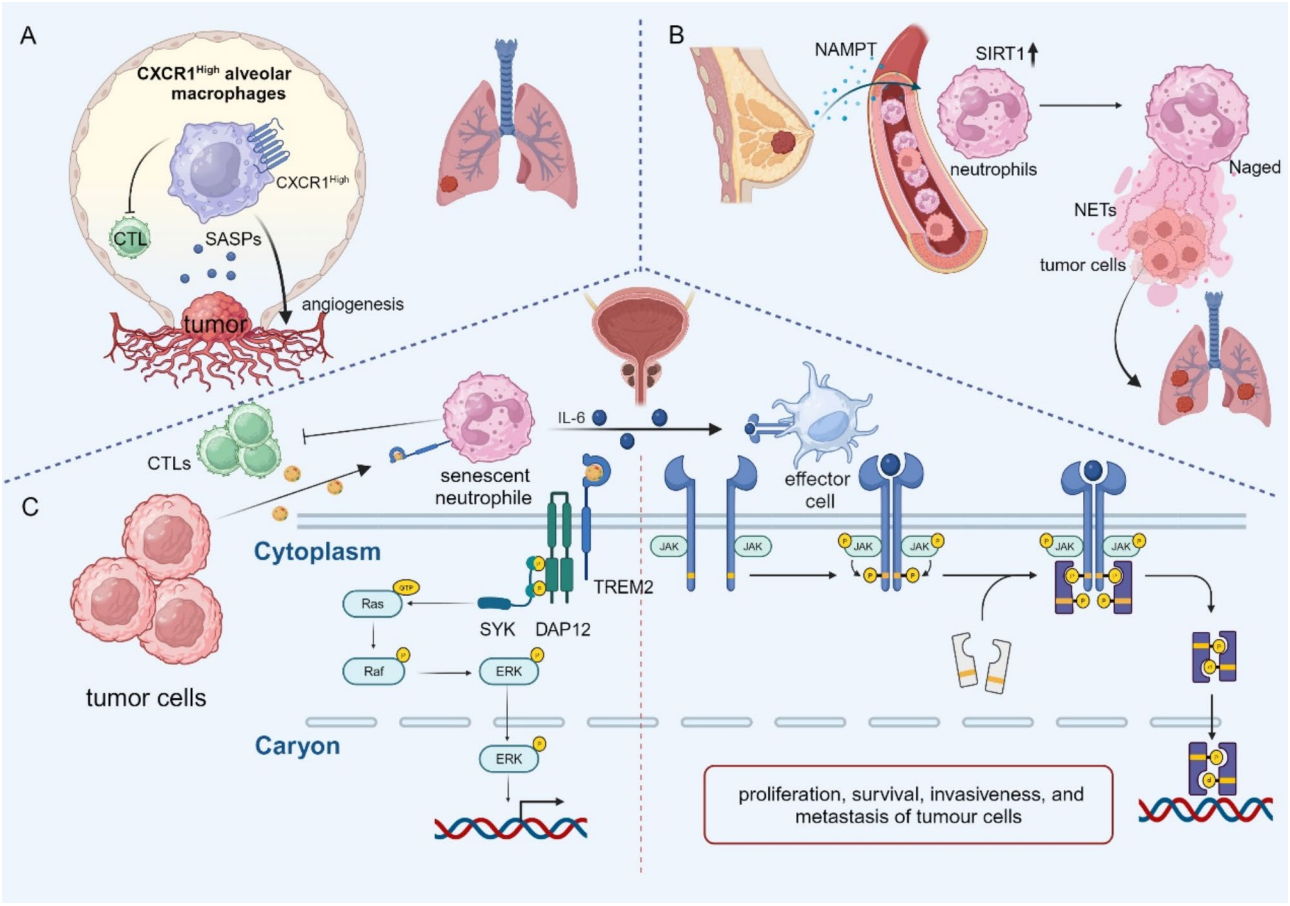

Fig. 3 The mechanism of immunosenescence promoting tumor occurrence and development. (**A**) Senescent alveolar macrophages inhibit CTLs, promote the release of SASP factors, and induce angiogenesis, thereby promoting the development of early-stage lung cancer; (**B**) Senescent neutrophils release NETs to capture tumor cells and promote breast cancer lung metastasis; (**C**) Senescent TREM2 + neutrophils exacerbate the progression of prostate cancer through the IL-6/JAK/STAT3 signaling pathway

and dysfunction of toll-like receptors (TLRs) [57, 58]. A study revealed the presence of senescent neutrophils within the microenvironment of prostate cancer, with their proportion showing a significant positive correlation with the progression of prostate cancer. Further investigation identified that apolipoprotein E (APOE), secreted by prostate cancer cells in a paracrine manner, binds to the triggering receptor expressed on myeloid cells 2 (TREM2) on the surface of neutrophils. This interaction activates the downstream DAP12/SYK/ERK signaling pathway, ultimately inducing neutrophil aging [59]. Senescent neutrophils inhibit the aggregation and activity of CD8 T cells [60] and secrete the inhibitory cytokines such as IL-6, which quickly activates the JAK/STAT3 signaling pathway [61–63], driving the proliferation, survival, invasiveness, and metastasis of tumor cells [64] (Fig. 3). Subsequent to the investigators' selective removal of senescent neutrophils, prostate cancer progression was significantly alleviated [59], further confirming that senescent neutrophils exacerbate prostate cancer progression. In another study, the researchers found that a group of new tumor-associated aged neutrophils (Naged) expressing $CXCR4^{high}CD62L^{low}$ accumulated in the lung premetastatic niche at early stage of breast tumorigenesis and promoted breast cancer lung metastasis. Mechanistically, breast cancer cells secrete Nicotinamide Phosphoribosyltransferase (NAMPT) to activate the expression of SIRT1 in neutrophils, thereby polarizing neutrophils into Naged. Naged opened mitochondrial permeability transition pore (mPTP) through SIRT1 to promote the release of mitochondrial DNA to form mitochondrion-dependent nonlethal neutrophil extracellular traps (NETs), and then NETs captured tumor cells to promote the retention of circulating tumor cells in lung tissue, thus promoting the breast cancer lung migration [65] (Fig. 3). Targeting the SIRT1-Naged-NETs axis was found to effectively reduce breast cancer lung metastasis in mice [65]. These findings demonstrate that cancer cells can induce neutrophil aging, driving tumor growth and metastasis in a vicious cycle. Targeting senescent neutrophils with senolytic therapies represents a promising avenue for cancer treatment.

DCs

Dendritic cells (DCs) serve as a critical link between innate and adaptive immunity. While aging does not significantly affect the number of DCs, it markedly impairs their antigen-presenting ability, phagocytic activity, chemotaxis, and capacity to produce IFN in elderly individuals [66], which greatly hinders the immune system's ability to recognize and eliminate cancer cells. Notably, defective chemotaxis and reduced cytokine production are key factors contributing to the impaired protective T cell responses associated with senescent DCs [66, 67]. Jonathan Kagan and colleagues demonstrated that a DC hyperactivator could correct age-related defects in DCs, induce cytolytic activity in CD4 + T cells, and ameliorate T cell-mediated anti-tumor immune deficiencies in aged mice, thereby promoting tumor eradication [68]. It also restored chemotaxis in aged DCs in the elderly [68], highlighting its potential as a promising future anti-tumor therapeutic agent.

Adaptive immune cells

T cells

Under normal conditions, naïve T cells mature in the thymus and migrate to lymphoid organs after antigenic stimulation, and differentiate into memory and effector T cells, essential for immune function. During immunosenescence, naïve T cells decline, memory T cells expand, and TCR diversity and homeostasis are disrupted [69]. Besides, aging is accompanied by the loss of the co-stimulatory molecules such as CD27 and CD28, which impairs the activation of CD8 + T cell [70]. Population-based studies have demonstrated that CD28 expression is significantly reduced in CD8 + T cell subsets in breast cancer patients, and this reduction can serve as an independent predictor of treatment prognosis [71, 72]. Furthermore, the expression of immune checkpoint-associated molecules, such as Tim-3 and TIGIT, increases with aging. Their immunosuppressive effects have been well-documented to contribute to tumor initiation and progression [73, 74]. The cytotoxicity of T cells is also diminished with age, as evidenced by decreased expression of IFN-γ, granzyme B, and perforin, which weakens their ability to kill tumor cells [75], which was confirmed in the breast cancer mouse models [76]. In addition, elevated expression of the killer cell lectin-like receptor subfamily G (KLRG)-1, CD57, and CD45RO, as well as increased expression of P16, P21, and P53 involved in cell cycle regulation are considered reliable markers of T-cell aging [77]. Metabolic alterations also accompany T cell aging, with senescent T cells preferentially relying on glycolysis for energy production. This metabolic shift leads to mitochondrial dysfunction and increased production of reactive oxygen species (ROS) [78, 79].

Current evidence suggests that Tregs accumulate progressively with aging [80], and their immunosuppressive properties may contribute to tumor development. Both experimental and clinical research have shown that Tregs levels are significantly higher in older individuals compared to younger ones, as observed in the Lewis lung cancer mouse model and in lung cancer patients [81]. T follicular helper cells (T_{FH} cells), which are present in lymphoid organs and peripheral blood, play a critical role in the humoral immune response. They highly express CD40 ligand (CD40L), which interacts with CD40 on B cells, facilitating B cell activation and antibody production [82]. However, during aging, T_{FH} cells exhibit reduced expression of CD40L, diminishing their ability to support B cells. This decline leads to a decrease in the production of protective antibodies [83], significantly impairing the anti-tumor efficacy of the humoral immune response.

B cells

B-cell-derived plasma cells are the exclusive producers of protective antibodies and play a pivotal role in both humoral and cellular immunity. As individuals age, the proportion of CD19 + B cells in peripheral blood decreases, B cell receptor (BCR) diversity diminishes, and BCR clonality increases [84]. Additionally, immunoglobulin class-switching recombination (CSR) and somatic hypermutation (SHM) are impaired, leading to reduced production of high-affinity antibodies [85]. Concurrently, aging-associated B cells (ABCs) accumulate and secrete autoantibodies and pro-inflammatory cytokines [86]. These age-related alterations collectively result in a decline in B cell immune function, increasing the risk of cancer and autoimmune diseases. Recent studies have revealed that ABCs accumulate in mice and transition into an age-associated clonal B cell (ACBC) state with age. Multi-omics analyses indicate that ACBCs exhibits a B-cell lymphoma phenotype characterized by elevated *Myc* expression in both elderly mice and humans, suggesting a potential origin of B-cell lymphoma [87, 88]. The administration of rapamycin has been shown to reduce ABC and ACBC levels, effectively extending the lifespan of mice. This finding highlights the potential of anti-aging compounds in cancer prevention or treatment [88]. Notably, José P. Castro's team discovered that ABCs accumulate in elderly patients at higher risk of B-cell lymphoma. Furthermore, clonal B cells enriched with ACBC phenotypic features were identified in individuals over 50 years old, providing strong support for the hypothesis that ACBCs also develop in humans [88].

The side effects of immunosenescence on ICIs

ICIs have shown strong efficacy in tumor immunotherapy, boosting survival rates for many cancer patients. However, their effectiveness declines in elderly patients, who also face more frequent irAEs. A meta-analysis of 5,393 patients revealed that anti-programmed death receptor 1 (PD-1)/programmed death ligand 1 (PD-L1) therapies improved survival in those under 75 (except melanoma patients) but offered no benefit for those over 75 [89]. A study on melanoma treatment in aged mice showed reduced anti-PD-L1 efficacy compared to young mice, linked to impaired DC migration, fewer CD8 + T cells, and fewer naïve T cells. DC overactivators corrected DC migration, induced cytotoxic CD4 + T cells, and improved anti-tumor responses, slowing melanoma progression [68]. Another study highlighted that tumors in both aged mice and patients with triple-negative breast cancer (TNBC) exhibited a lack of genes associated with antigen presentation, inflammation, and IFN response pathways. This suggests impaired activation of CD8 + T cells, and the application of ICIs failed to elicit anti-tumor immune responses in elderly mice. These findings indicate that age-related immune dysfunction limits the effectiveness of ICIs in treating TNBC [76]. In a separate experiment, the therapeutic effect of anti-PD-L1 on colon cancer and lymphoma was significantly lower in aged mice compared to young mice. Mechanistically, aging induces an immunosuppressive TME through myeloid CD11b + cells, which restricts the expansion and activation of CD8 + T cells within the tumor, driving resistance to anti-PD-L1 therapy [90]. Combination therapy involving ICIs and chemotherapy (ICI-chemotherapy) is now the standard treatment for non-small cell lung cancer (NSCLC) without targeted oncogene alterations. However, an analysis of overall survival (OS), progression-free survival (PFS), and safety in 1,245 NSCLC patients revealed that ICI-chemotherapy did not improve survival rates in patients aged 75 years and older, while increasing the incidence of grade 3 or higher irAEs in this age group [91]. Given the high incidence of tumors in the elderly population and their reduced sensitivity and increased vulnerability to ICIs treatment, it is crucial to investigate the impact and underlying mechanisms of ICIs therapy in older patients. However, there is currently limited data on ICIs treatment specifically related to elderly patients. Therefore, further experimental and clinical research is essential to expand the available data and elucidate the mechanisms involved, ultimately improving therapeutic outcomes for this demographic.

Treatment strategies for immunosenescence

Given the role of immunosenescence in promoting tumor progression and its potential to compromise the efficacy of ICIs, there is an urgent need to identify methods and strategies to mitigate or even reverse immunosenescence.

Importing "youthful ingredients" to alleviate or reverse immunosenescence

Thymus involution results in a decline in T cell production, contributing to immunosenescence. Therefore, restoring the structure and function of the thymus has the potential to mitigate or even reverse this age-related immune decline. Research has demonstrated that transplanting young thymic epithelial cells into middle-aged individuals with thymic degeneration can promote thymic regeneration and increase T cell production [92]. *FoxN1*, an epithelial cell-autonomous gene expressed in the thymic epithelium, plays a critical role in regulating thymogenesis and T cell development. Introducing *FoxN1* into the thymus of aged mice has been shown to partially alleviate thymic degeneration and restore T cell populations [93]. In addition, IL-21, which exhibits significant thymic trophic properties [94], and regular physical activity may also support thymic function [95]. In a more direct approach, injecting young immune cells into aging mice has been observed to reverse immunosenescence to some extent [96]. Long-term antigen stimulation can cause aging of CD8 T cells in mice. However, reintroducing "healthy and young" CD4 T cells can restore the proliferative capacity and cytokine production of aged CD8 + T cells. Furthermore, combining CD4 + T cell therapy with ICIs enhances the functional recovery of CD8 T cells [97]. With advancing age, the composition of hematopoietic stem cells (HSCs) shifts from those with balanced lymphoid and myeloid output (bal-HSCs) to those with a myeloid-biased output (my-HSCs). This shift reduces lymphocyte production and increases myeloid cell production, exacerbating immunosenescence. Depleting my-HSCs through antibody therapy has been shown to significantly increase the population of bal-HSCs and their progeny, which are essential for maintaining a "youthful" immune system. Moreover, aged mice treated with this antibody therapy exhibited reduced lymphocyte aging phenotypes and lower levels of chronic inflammation-related cytokines. These mice also demonstrated improved resistance to infections and enhanced vaccine efficacy [98]. These findings highlight that direct or indirect interventions involving "youthful components" can alleviate or even reverse immunosenescence, offering promising avenues for therapeutic strategies aimed at restoring immune function in aging individuals.

Eliminating aging immune cells or tumor cells

The senotherapeutic strategy, which includes the selective elimination of senescent cells using senolytics, is currently a widely adopted approach for delaying aging. A senolytic combination of D + Q has been shown to effectively clear senescent cells in mice, significantly improving their survival rates [99]. This combination has already been employed as a senolytic strategy for certain diseases in clinical practice [100]. However, emerging evidence highlights significant limitations, such as low selectivity, potential off-target effects, and adverse reactions, which hinder its broader application [7, 8]. As a result, there is a pressing need for innovative senolytics with higher selectivity, improved efficacy, and reduced adverse effects. Due to its unique physicochemical properties, nanotechnology can deliver and release drugs to aging cells, optimizing clearance effects. β_2-microglobulin (B2M) has been identified as a marker of cellular aging [101]. Molecularly imprinted nanoparticles (nanoMIPs) loaded with dasatinib showed strong selective killing ability against B2M + senescent cells and improved efficacy compared to using dasatinib alone, reducing dasatinib's off-target toxicity [102]. In another innovative approach, Zhang et al. developed a "double locks-like" nanoplatform that integrates Galactan coating and mesoporous polydopamine to encapsulate drug D + Q. In this way, high-loading D + Q can only be released continuously to senescent cells with high expression of β-gal and low PH value, specifically eliminating senescent cells without affecting normal cells, and showing amazing effects in preventing the growth and metastasis of breast cancer [103].

Navitoclax (ABT-263) targets and inhibits anti-apoptotic Bcl-2 family members, selectively leads to apoptosis of senescent cells [104], and even effectively kills senescent ovarian and breast cancer cells [105]. However, Navitoclax may lead to thrombocytopenia, which limits its clinical application [106]. Galacto-conjugated nanoparticles with navitoclax (nav-gal) render Navitoclax inactive in its prodrug form, only becoming active when the galactose portion is cleaved by SA-β-gal, which is highly expressed in senescent cells. This not only reduces the toxicity of Navitoclax but also enhances its selectivity towards senescent cells [107].

CAR-T cells represent a groundbreaking anti-cancer therapy that utilizes genetically engineered T cells to recognize and target tumor cells. In recent studies, CAR-T cells have been modified to recognize surface proteins of senescent cells and eliminate senescent cells. Researchers have found that natural killer group 2 member D ligands (NKG2DLs) are highly expressed in senescent cells and can assist senescent cells in evading immune clearance by NK cells. They designed NKG2D-CAR-T cells targeting NKG2DLs, which can effectively and selectively kill NKG2DLs + senescent cells in nonhuman primates without observing any adverse reactions [108]. Further studies have revealed that NKG2DLs are also overexpressed in tumor cells [109, 110]. NKG2D-CAR-T cells can target and clear NKG2DL + tumor cells *in vitro and in vivo*, thereby achieving tumor suppression effects [109, 110]. Urokinase plasminogen activator receptor (uPAR) is also a surface protein of senescent cells. uPAR-CAR-T cells can selectively kill senescent cells in tumors, significantly delaying the development of lung adenocarcinoma without causing detectable toxicity [111]. More importantly, a single administration is sufficient to achieve long-term therapeutic and preventive effects [112]. Although NKG2D-CAR-T cells and uPAR-CAR-T cells have shown a favorable safety profile in preclinical trials, their safety and potential toxicity in the elderly must be thoroughly investigated through clinical trials. In conclusion, these findings suggest that CAR-T cells targeting senescent cells may be effective immune cell-based senolytics.

Telomere shortening and reduced telomerase activity are closely associated with the development of age-related diseases. Studies have demonstrated that after the use of Hyperbaric Oxygen Therapy (HBOT) can significantly lengthen telomeres and enhance the clearance of senescent immune cells [113]. In addition, an increase in telomerase activity can enhance the replication ability of T cells, thereby enhancing T cell-related immune responses and exercising anti-tumor functions [114]. Notably, researchers have developed a chimeric mouse model, termed "hyper-long telomere mice," which exhibits longer telomeres compared to normal mice. These mice demonstrate a reduced incidence of cancer, delayed aging, and an extended lifespan [115]. However, the relationship between telomere length and lifespan is complex. A recent study challenges the idea that "extending telomeres equals extending lifespan", revealing that *POT1* gene mutations, which cause abnormally long telomeres, are linked to a higher incidence of tumors, including thyroid cancer, melanoma, and lymphoma [116]. Therefore, maintaining telomere length within an optimal range represents both a critical and challenging objective.

Mitigating the production of inflammatory factors

Another approach within the senotherapeutic strategy involves reducing the production and secretion of SASP factors using senomorphics. The NF-κB-mediated signaling pathway is a primary regulator of the pro-inflammatory effect of SASPs. Metformin has been shown to inhibit the NF-κB pathway to some extent, thereby reducing the expression of various SASP factors and exerting both anti-aging and anti-tumor effects [117]. Similarly, rapamycin, an inhibitor of mammalian target of the rapamycin (mTOR), reduces NF-κB activity, thereby inhibiting pro-inflammatory SASP factors, achieving

Table 1 List of current drugs targeting immunosenescence

Senotherapeutic drugs	Targets	Ameliorable diseases in vivo	References
Dasatinib + Quercetin	Tyrosine kinase	Ovarian cancer	[120]
Navitoclax	Bcl-2 family	Ovarian and breast cancer	[105]
Nav-gal	Bcl-2 family	Lung cancer	[107]
uPAR-targeted CAR T cells	uPAR	Lung adenocarcinoma	[111]
Rapamycin	mTOR	Breast cancer	[121]
		Lung cancer	[122]
		Skin cancer	[123]
Metformin	NF-κB pathway	Breast cancer	[124]
		Colon cancer	[125]
		Prostatic cancer	[126]
		Ovarian cancer	[127]

prevention of aging, and limiting tumor growth [118]. Notably, the senotherapeutic strategy is an emerging strategy for combating immunosenescence that has been demonstrated in in vivo experiments to have significant benefits for a wide range of cancers (Table 1). Therefore, it is crucial to further investigate how to translate these interventions into human clinical trials and accelerate their widespread application. Recently, researchers have found that aging enhances emergency myelopoiesis, leading to the accumulation of myeloid progenitor-like cells in lung cancer, which are the main source of the inflammatory cytokine IL-1 and cause lung cancer progression. The use of IL-1R1 antagonist anakinra can not only slow down the progression of lung cancer, but also normalize emergency myeloid cell generation in elderly mice, fundamentally eliminating immunosenescence [119].

Conclusions

Immunosenescence is a complex, multifaceted, and inevitable process closely associated with aging. It is influenced by factors such as antigenic stimulation and chronic inflammation, leading to immune dysfunction. This dysfunction is linked to tumor development and the diminished efficacy of ICIs in achieving the desired immune response. Concurrently, immunosenescence results in characteristic alterations in immune cell subpopulations, including imbalances in quantity and proportion, variations in surface molecule expression, and metabolic changes. These alterations collectively serve as markers of immunosenescence and can be utilized for cancer screening, prevention, and subsequent intervention. Current cancer intervention strategies targeting immunosenescence primarily focus on reversing the causes or triggers of immunosenescence and eliminating already senescent immune cells. Results from related clinical trials have been positive and effective. However, numerous aspects of the relationship between immunosenescence and tumors remain to be explored. First, the mechanisms underlying the poor efficacy of ICIs and the occurrence of irAEs in elderly patients are not yet fully understood and require further investigation. Second, there is a need to quantify the markers of immunosenescence and establish reference ranges for different age groups to enhance the accuracy and specificity of the screening and intervention for diseases such as cancer. Thirdly, while significant progress has been made in anti-aging treatments, their adverse reactions and off-target effects remain critical challenges that can compromise their efficacy in cancer therapy. Fourthly, CAR-T cell therapy highly relies on functionally active T cells; however, T cell aging contributes to the immunosenescence of CAR-T cells, resulting in reduced efficacy in targeting hematological malignancies [128]. Several studies have confirmed that CAR-T cell therapy is most effective in treating hematological malignancies in children and young adults, with complete response (CR) rates reaching up to 90% [129]. In contrast, for patients over the median age of 70, the CR rate drops significantly, ranging from 33 to 73% [130, 131]. The safety of CAR-T cell therapy cannot be ignored, and the most common adverse reactions after treatment are hematological toxicity, including neutropenia, leukopenia, anemia and thrombocytopenia [132], as well as infection complications [133, 134]. In summary, a deeper understanding of the impact of immunosenescence on cancer progression is essential. Establishing more accurate models of immunosenescence will provide valuable insights into anti-aging immunity and cancer therapy, paving the way for more effective and targeted treatments.

Abbreviations

AIS	Adenocarcinoma in situ
APOE	Apolipoprotein E
ABCs	Senescence-associated B cells
ACBC	Age-associated clonal B cell
BCR	B cell receptor
B2M	β_2-microglobulin
bal-HSCs	HSCs with balanced output of lymphoid and myeloid cells
CR	Complete response
CSR	Class-switching recombination
CTL	Cytotoxic T cells
CAR	Chimeric antigen receptor
DNMT3A	DNA methyltransferase 3 A
DDR	DNA damage response
DCs	Dendritic cells
D + Q	Dasatinib and quercetin

ERK1/2	Extracellular regulatory protein kinase 1/2
HBOT	Hyperbaric Oxygen Therapy
IMD	Immune deficiency
ICIs	Immune checkpoint inhibitors
irAEs	Immune-related adverse events
IL	Interleukin
IFN	Interferon
KIRs	Killer-cell Immunoglobulin-like Receptors
KLRG	Killer cell lectin-like receptor subfamily G
MHC	Major histocompatibility complex molecules
mPTP	Mitochondrial permeability transition pore
mTOR	Mammalian target of rapamycin
my-HSCs	HSCs with myeloid-biased output
nanoMIPs	Molecularly imprinted nanoparticles
NK cells	Natural killer cells
Naged	Tumor-associated aged neutrophils
NAMPT	Nicotinamide Phosphoribosyltransferase
NETs	Neutrophil extracellular traps
NSCLC	Non-small cell lung cancer
NKG2DLs	Natural killer Group 2 member D ligands
OS	Overall Survival
PFS	Progression-Free Survival
pDCs	Plasmacytoid dendritic cells
PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand 1
rPGRP-LC	Regulatory PGRP-LC
ROS	Reactive oxygen species
Syx13	Syntaxin 13
S6K	S6 kinase
STAT1/3	Signal transduction and transcriptional activator 1/3
SASPs	Senescence-associated secretory phenotypes
SA-β-gal	Senescence-associated β-galactosidase
SHM	Somatic hypermutation
Th cells	Helper T cells
TNF-α	Tumor necrosis factor-α
TGF-β	Transforming growth factor-β
Treg cell	Regulatory T cell
T_{FH} cells	T follicular helper cells
TORC1	Target of Rapamycin Complex 1
TREM2	Triggering receptor expressed on myeloid cells 2
TNBC	Triple-negative breast cancer
TME	The tumor microenvironment
TLR	Toll-like receptor
TCR	T cell receptor
uPAR	Urokinase plasminogen activator receptor

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

Declarations

Conflict of interest
The authors declare that they have no competing.

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