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Review article

Impact of immunosenescence and inflammaging on the effects of immune checkpoint inhibitors

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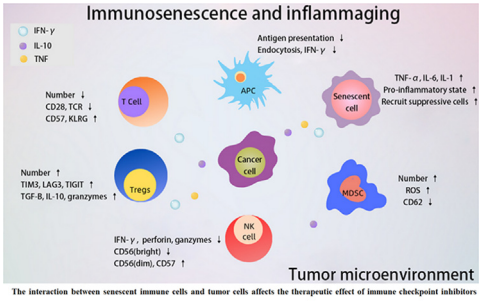
HIGHLIGHTS

- Immunosenescence changes the frequency and function of immune cells.
- Inflammaging leads to an imbalance between inflammation and anti-inflammation.
- Immunosenescence and inflammaging result in a dysfunctional immune response and an unbalanced inflammatory status, which eventually affects the effectiveness of immune checkpoint inhibitors.

GRAPHICAL ABSTRACT



The interaction between senescent immune cells and tumor cells affects the therapeutic effect of immune checkpoint inhibitors (ICIs). In tumor microenvironment (TME), senescent immune cells produce pro-inflammatory cytokines and recruit immunosuppressive cells, leading to the dysfunction of immune response in TME. Senescent immune cells eventually lead to a decline in the efficacy of immune checkpoint inhibitors and an increase in immune-related adverse events (irAEs) by upregulating immune checkpoint receptors and producing immunosuppressive TME. APC: Antigen-presenting cells; CD: Cluster of differentiation; IFN: Interferon; IL: Interleukin; KLRG: Kill cell lectin-like receptor; LAG3: Lymphocyte-activation gene 3; MDSC: Myeloid-derived suppressor cell; NK: Natural killer; ROS: Reactive oxygen species; TCR: T cell receptor; TGF: transforming growth factor; TIGIT: T cell immunoreceptor with Ig and ITIM domains; TIM3: T cell immunoglobulin domain and mucin domain-3; TNF: Tumor necrosis factor; Tregs: Regulatory T cells.

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are employed in immunotherapeutic applications for patients with weakened immune systems and can improve the ability of T cells to kill cancer cells. Although ICIs can potentially treat different types of cancers in various groups of patients, their effectiveness may differ among older individuals. The reason ICIs are less effective in older adults is not yet clearly understood, but age-related changes in the immune system, such as immunosenescence and inflammation, may play a role. Therefore, this review focuses on recent advances in understanding the effects of immunosenescence and inflammation on the efficacy of ICIs.

Introduction

The human lifespan has increased in recent decades[1]; however, people over 75 years of age are more prone to cancer.[2] Radiotherapy and chemotherapy, which are conventional methods for treating cancer, are less effective than immunotherapy because of their lower specificity and significant side effects. The development of immunotherapy has expanded the treatment options for older patients with cancer and has improved overall survival (OS) rates. The use of immune checkpoint inhibitors (ICIs) has led to significantly improved clinical

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responses in the treatment of several types of solid cancers.[3] In terms of immunotherapy, the efficacy of ICIs can be affected by a patient's immune status. Older adults may experience significant changes in their immune system, such as immunosenescence and inflammation, which can affect the effectiveness of ICIs.[4] Although ICIs have been successful, the use of these drugs has been hindered by patient resistance and such treatment can be impeded by adverse immune-related events, especially among older patients.[5]

Immunosenescence and inflammaging

Aging is a complex biological process that affects the functions of multiple organs and increases the susceptibility of older individuals to age-related diseases.[6] Immunosenescence refers to the significant changes that occur in the immune system as an individual ages, which can lead to the restructuring of lymphoid organs and changes in the immune function of older adults.[7] Immunosenescence affects both innate and adaptive immunity and can result in a pro-inflammatory state. With aging, the levels of cytokines in the human peripheral circulation increase, leading to a chronic and low-grade inflammatory state, which is called inflammaging. Additionally, the capacity for generating sufficient immune responses gradually declines owing to immunosenescence.[8] Inflammation represents a significant factor in the development and progression of age-related diseases and is often characterized by the coexistence of multiple conditions in older people.[9] Immunosenescence can reduce the efficacy of immunotherapy and lead to poor treatment outcomes. For instance, a meta-analysis revealed that patients aged ≥65 years (hazard ratio: 0.71) were more likely to derive OS benefits from immunotherapy than patients over the age of 75 years (hazard ratio: 1.23), potentially due to the effects of immunosenescence and inflammaging.[10] Immunosenescence may contribute to ICI outcomes in older patients. One study found that a higher percentage of senescent T cells was associated with poorer treatment outcomes in patients administered ICIs than in those who received platinum-containing chemotherapy (PCT). This finding suggests that immunosenescence may contribute to the reduced efficacy of ICIs in older patients.[11] The proportion of senescent T cells may reflect a person's biological age and could be an important factor in determining the effectiveness of ICIs. Below, we examine how immunosenescence and inflammation individually impact ICIs and explore potential biological markers that could predict the suitability of ICIs for older patients.

Immunosenescence and cancer

The role of the immune system in cancer is complex and not fully understood, as it plays critical roles in both antitumor responses and immune evasion. Thus, the immune system is closely associated with cancer development and progression.[12] The results of numerous studies have indicated that the antitumor responses in younger patients differ from those in older patients.[7] However, the mechanisms underlying the differences in the antitumor responses between younger and older patients are not yet fully understood. T cells are critical components of the immune system and serve as the basis whereby ICIs effectively target and eliminate tumor cells. As individuals age, T cells undergo significant changes that can lead to deficiencies in the immune system, which increases their susceptibilities to age-related diseases and elevates the incidence of cancer in older individuals.[13] Thus, tumor occurrence is intricately linked to immunosenescence. In addition, senescent T cells upregulate the expression of immune checkpoint receptors and increase programmed cell death ligand 1 (PD-L1) expression in tumor cells.[14,15]

Different viewpoints exist regarding the relationship between chronological age and the occurrence of malignant tumors. While some researchers believe that the incidence of tumors increases with age, others posit that immunosenescence is closely associated with tumor development. The results of a study conducted to investigate the incidence of cancer in older people showed that individuals over the age of 60 years were more susceptible to cancer, with the highest incidence occurring in individuals between the ages of 65 and 69 years.[16] After analyzing the age of patients with various types of cancer, researchers concluded that the immune system plays a crucial role in tumor development.[17] In addition, senescent T cells, described as cluster of differentiation $CD28^{-}CD57^{+}$ cells, are related to the cancer stage and a poor treatment response. One possible explanation for these observations is that CD28, a co-stimulatory molecule, is indispensable for immunotherapeutic interventions.[18] The T cell receptor (TCR) repertoire significantly diminishes with age, particularly after the age of 65. This reduction may weaken the specific immune responses of T cells against target tumor antigens.[18] Furthermore, immunosenescence may lead to the accumulation of cells with inhibitory functions such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[19] These cells secrete cytokines, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which can suppress antitumor responses. Below, we summarize the mechanisms and signaling pathways underlying the effects of immunosenescence and inflammation on immune and tumor cells [Figure 1].

Furthermore, preclinical and clinical data have demonstrated that immunosenescence can facilitate tumor development. Senescent $CD8^{+}$ T cells play critical roles in breast cancer pathogenesis and treatment in patients.[20] $CD8^{+}$ T cells in old mice, more prone to breast cancer, produce less interferon (IFN) than young.[21]

Impact of T cell senescence on immune checkpoint inhibitors

ICIs function by removing inhibitory brakes on T cells, leading to robust activation of the immune system and the generation of sufficient antitumor immune responses. T cells are the primary targets of ICIs, and changes in the proportion of senescent T cells can affect their efficacy. In the following section, we examine how senescent T cells affect the effectiveness of ICIs that target immune-inhibitory receptors such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and PD-L1.

Changes of T cell receptor

TCR diversity enables effective cellular immune responses to a wide range of unknown pathogens. However, the diversity of TCRs in both naïve $CD4^{+}$ and naïve $CD8^{+}$ T cells tends to decrease with age in older individuals.[22] A recent report demonstrated that the TCR diversity was significantly lower in naïve $CD8^{+}$ T cells, whereas memory $CD8^{+}$ T cells displayed higher clonal expansion and a marked increase in the retention of TCR sequences.[23] Owing to such changes in the TCR diversity, the ability of $CD8^{+}$ T cells to recognize cancer cells may decrease with aging, even if ICIs are used to reactivate T cells. Following puberty in adults, the thymus undergoes progressive degeneration, leading to a significant decline in the T cell pool, a reduction in TCR diversity, and a continuous decrease in the number of T cell exportation. Consequently, immunosenescence reduces the immune activities of effector T cells and memory T cells.[24] PD-1 is a member of the CD28 family that generates negative signals after TCR triggering.[25] Although PD-1 antibodies can activate senescent T cells, defective TCRs may not produce a sufficient immune response in older patients as they would in younger individuals. Conversely, chronic antigenic stimuli encountered throughout one's lifetime can lead to the generation of a clonal T cell memory pool and an increased abundance of clonal TCRs, as observed in older adults following cytomegalovirus (CMV) infection.[24] The expansion of clonal TCRs can also lead to a decreased ability to recognize tumor cells.

Decreased T cell abundances in older people

Ample evidence suggests that the thymus plays critical roles in the differentiation, development, and maturation of T cells. Thymic atrophy, which is commonly observed in older individuals, can lead to a reduction

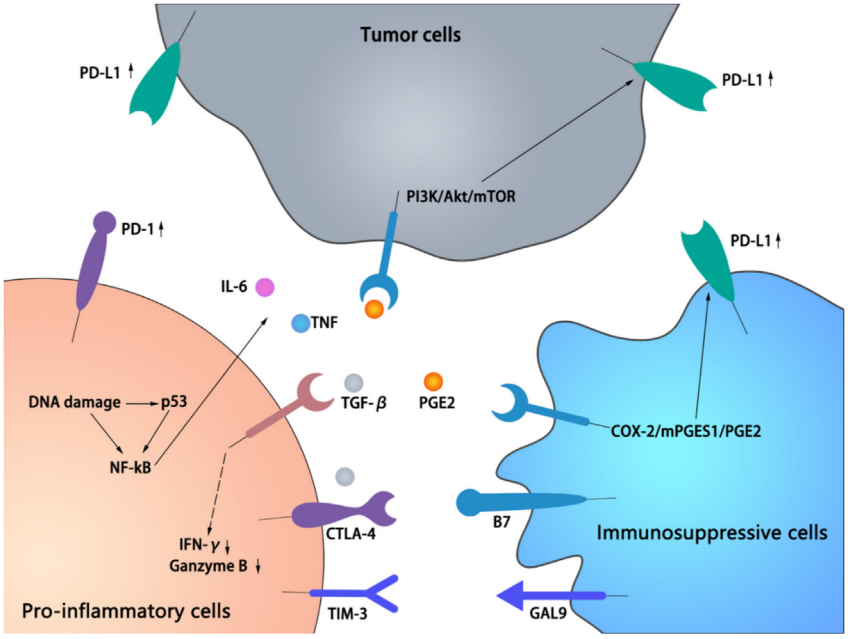

Figure 1. The influence of immunosenescence and inflammaging on immune and tumor cells. The main pro-inflammatory cells are T cells and NK cells that decrease the secretion of IFN-γ and granzyme B through the NF-κB pathway, but upregulate the expression of immune checkpoint receptors (such as PD-1, CTLA-4, and TIM3). Immunosuppressive cells (such as Tregs, MDSCs, and macrophages) express high levels of PD-L1 after COX-2/mPGES1/PGE2 pathway activation and signaling through a B7 protein and GAL9, which inhibits T cells function. In tumor cells, PGE2 upregulates PD-L1 expression by activating the PI3K/Akt/mTOR pathway. AKT: Protein kinase B; COX-2: Cyclooxygenase 2; CTLA-4: Cytotoxic T lymphocyte-associated protein 4; DNA: Deoxy ribonucleic acid; GAL9: Galectin 9; IFN: Interferon; IL: Interleukin; MDSCs: Myeloid-derived suppressor cells; mPGES1: Microsomal prostaglandin E synthase 1; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor-kappa B; NK: Natural killer; PD-1: Programmed cell death 1; PD-L1: Programmed cell death ligand 1; PGE2: Prostaglandin E2; PI3K: Phosphoinositide 3-kinase; TGF-β: Transforming growth factor-beta; TIM3: T cell immunoglobulin and mucin-domain containing 3; TNF: Tumor necrosis factor; Tregs: Regulatory T cells.

in the number and proportion of $CD8^+$ naïve T cells and is associated with age-related diseases.[26] This phenomenon is very common in humans and other vertebrates.[27] The thymic output of naïve T cells is significantly lower, which reduces the diversity of the TCR repertoire, culminating in disrupted T cell homeostasis.[28,29] $CD8^+$ T and natural killer (NK) cells are crucial for antitumor immunity. Indeed, an increased frequency of circulating lymphocytes was related to treatment outcomes and increased OS in melanoma patients receiving ICIs.[30,31] Moreover, a higher number of effector and memory $CD8^+$ T cells was associated with favorable outcomes. However, the number of effector T cells tends to decrease with age.[32] The results of one study demonstrated that patients with advanced melanoma who were treated with ICIs and had more circulating $CD8^+$ effector cells exhibited better treatment outcomes and longer OS.[33] Similarly, a decreased frequency of circulating $CD4^+$ T cells was associated with a shortened OS.[30] In summary, immunosenescence can reduce the effectiveness of ICIs by decreasing the frequency of T cells in older individuals.

Phenotype of senescent T cells

The phenotypes of T cells change with age, and senescent T cells are primarily associated with reduced proliferative activity.[34] T cell senescence is typically characterized by decreased CD28 expression, increased CD57, and kill cell lectin-like receptor (KLRG) expression, and a lower proliferative capacity along with shortened telomeres. Additionally, senescent T cells often have a reduced ability to recognize antigenic diversity.[11] CD28 is an essential co-stimulatory molecule that activates the mammalian target of rapamycin complex 1 (mTORC1) pathway and several transcriptional activators to induce T cell activation.[35] CD28 plays a crucial role in T cell function, including increasing the expression of IL-2 and IL-3 to activate cytotoxic T cells and binding with CD80 to stimulate B cells.[35] CTLA-4, an inhibitory receptor expressed only on T cells, has a stronger affinity than CD28 for the same ligands (CD80 and CD86).[5] Thus, on the surface of senescent T cells, downregulation of CD28 and the presence of CTLA-4 can result in T cell immunosuppression, even in patients undergoing anti-CTLA-4 immunotherapy.

Senescent T cells with the $CD28^-CD57^+KLRG^+$ phenotype are referred to as having the senescent immune phenotype (SIP). Persistent antigenic stimulation, such as that from CMV, can lead to the accumulation of senescent T cells that exhibit a low replicative capacity, pro-inflammatory behavior, and oligoclonal characteristics.[36] T cells with a SIP may negatively affect the efficacy of ICIs in older patients. Recent flow cytometric data indicated that the SIP was associated with the efficacy of ICI therapy, according to the percentages of circulating T cells with the SIP from patients treated with ICIs or PCT.[11] In that study, a higher frequency of SIP^+ T cells correlated with a worse objective-response rate, the median progression-free survival rate, and the median OS. Conversely, the results of another clinical study showed that a higher frequency of circulating $CD45R^-CCR7^-CD27^+CD28^+$ effector memory T cells in patients with advanced melanoma was associated with improved treatment outcomes.[37] Senescent T cells showed low proliferation even after TCR/CD28 engagement. Although they released increased levels of IFN-γ and tumor necrosis factor (TNF), senescent T cells barely produced IL-2, indicative of a secretory phenotype associated with senescence that was characterized by a significant increase in the secretion of pro-inflammatory cytokines.[38,39]

In a previous study, researchers discovered that intratumoral $CD8^+$ T cell levels in patients with lung cancer were shifted by senescence in older individuals (median age of 72 years) without lung cancer.[40] This phenomenon is often observed in patients with advanced tumors (indicating that the SIP is associated with tumor development) and has been associated with a lower $CD4^+$: $CD8^+$ T cell ratio and a higher percentage of $CD28^-CD57^+$ senescent T cells. Thus, tumor growth can cause SIP, which can contribute to tumor development and affect the effectiveness of ICIs.[41] In summary, the frequency of $CD8^+CD28^-$ T cells not only affects the development of tumors but also leads to a decline in the effectiveness of ICIs. However, the relationship between the expression of CD57 in $CD8^+$ T cells and the therapeutic effect of ICIs is controversial. CD57 expression enhances the cytotoxicity of T cells by promoting the expression of IFN-γ, granzyme B, and perforin.[42] One study showed that $CD8^+CD57^+$ T cells in tumors displayed a worse response when treated with anti-PD-1.[42] However, another study found a high frequency of $CD8^+CD57^+$ T cell was observed in patients with metastatic urothelial cancer who responded to anti-PD-1.[43] Furthermore, after surgery in patients with resectable head and neck squamous cell carcinomas, the percentage of $CD57^+$ cells decreased to a lower level.[44] The presence of more $CD8^+CD57^+$ T cells in circulation has been linked to the sustained response of T cells to tumors.[43] The varying outcomes related to the expression of CD57 may be due to the different locations of $CD57^+$ T cells, and there may be diversity in $CD57^+$ T cells across different cancer types.

Increasing number and enhanced function of regulatory T cells

Tregs play a crucial role in maintaining a balanced immune response by preventing excessive immune activation and suppressing responses to self-antigens.[45] The classic phenotype of Tregs is that they express CD4 as well as the Forkhead Box P3 (Foxp3) protein, which can directly or indirectly regulate the immune system. For example, Tregs can express IL-10 to repress the function of leukocytes, antigen presentation, secondary signals of T cell activation, and T cell expansion.[46] In addition, Tregs can suppress effector T cells by producing cytotoxic molecules that induce apoptosis of effector T cells.[45] In older adults, chronic inflammation requires increased immunosuppressive activity to stabilize the inflamed microenvironment. However, the functions of Tregs are unchanged or enhanced in older individuals (who are more susceptible to infections and malignant tumors), suggesting that their functions become stronger with age.[47] Despite the occurrence of thymus involution in older people, the number of Tregs increases due to the loss of the pro-apoptotic protein Bim in Tregs.[48]

A relationship exists between Tregs and the efficacy of ICIs. In most types of cancer, a decrease in the ratio of $CD8^+$ T cells to Tregs in tumors is associated with a poor prognosis. Evidence exists that ICI therapy can decrease the frequency of Tregs, which reduces the inhibition of effector T cells and thereby enhances their functions.[49] However, many patients who respond initially to ICIs develop drug resistance. A possible reason for this acquired resistance is that the suppressive function of Tregs can help cancer cells resist the effects of ICIs over time.[50] Immunosenescence may lead to an increase in the number of Tregs and enhance Treg function, which may contribute to acquired resistance and poorer treatment outcomes.[51] As individuals age, Tregs express higher levels of other immune checkpoint receptors, including T cell immunoglobulin domain and mucin domain-3 (TIM-3), lymphocyte-activation gene 3 (LAG-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT), which suppress the activation of effector T cells and enhance the inhibitory function of Tregs. Additionally, the upregulation of these receptors enhances the suppressive function of Tregs by increasing their expression levels of TGF-β, IL-10, granzymes, and perforin.[50] Moreover, elevated TGF-β expression can promote cancer development, increase the frequency of Tregs, and inhibit T cell activity by downregulating IFN-γ and granzyme B via phosphorylation of the Smad 2/3 protein and inhibition of mitochondrial respiration.[50,52] Cellular senescence may lead to increased secretion of suppressor cytokines by Tregs, thereby enhancing their ability to suppress immune responses.[53]

It is traditionally assumed that patients with lower Treg levels in the blood and tumor microenvironment (TME) will respond better to ICI therapy. However, researchers have discovered that patients who received ICIs exhibited better outcomes and had an increased number of Tregs in their lymph node metastases than those with fewer Tregs[54] which challenges conventional beliefs. The results of another study supported this viewpoint, indicating that patients with a higher frequency of circulating Tregs responded better to anti-CTLA-4 treatment.[30] In addition, Woods et al. found that patients with an increased proportion of Tregs in the peripheral blood showed good responses to anti-PD-1 treatment.[55] One explanation for this phenomenon could be that the number of effector T cells was overlooked. Therefore, assessing the ratio of $CD8^+$ effector T cells to Tregs, rather than simply the number of Tregs, may provide an effective way to predict the efficacy of ICIs in older individuals.

Impact of senescent natural killer cells on immune checkpoint inhibitors

NK cells are members of the innate immune system that can respond to viral infection and/or transformed cells and have multiple immune functions, mainly involving the cytotoxicity and expression of numerous cytokines.[56,57] NK cells often express many immune checkpoint receptors such as CTLA-4, PD-1, killer immunoglobulin-like inhibitory receptors (KIRs), and LAG-3.[58–61] The subset frequency and function of NK cells are related to ICI-treatment outcomes.[62] Typically, NK cells induced by tumors have upregulated PD-1 expression, which impairs their ability to elicit an effective antitumor response.[61] The recruitment and cytotoxicity of NK cells against tumor cells can be increased by PD-1/PDL-1 inhibitors.[63] Furthermore, ICI therapies can potentially activate NK cells and upregulate IFN-γ expression.[64] However, as individuals age, NK cell dysfunction becomes more common and is associated with increased risks for infections, malignant tumors, inflammatory diseases, and cellular aging.[65] Immunosenescence can lead to age-related changes in NK cell functions, characterized by reduced abilities to release cytokines and induce apoptosis in tumor cells.[65] For instance, senescent NK cells may bind to IL-2, but they release lower levels of IFN-γ[66] and age-related NK cell dysfunction can reduce perforin and granzyme expression.[67] Therefore, NK cell cytotoxicity is reduced by cellular senescence, which is associated with an increased risk of developing cancer.[68] Although aging does not typically affect the frequency of NK cells, it can alter the proportion of NK cell subsets and their cytotoxicity.[69,70] In terms of NK cell subsets, the population of CD56 (bright) cells tended to decrease in older individuals, whereas the number of CD56 (dim) subsets increased. Additionally, the observation of CD57 upregulation suggests that NK cells become highly differentiated with age.[71] These alterations in NK cells are related to their dysfunction and lack of proliferation. Therefore, in older individuals, the ability to eliminate senescent and tumor cells declines, resulting in impaired immune surveillance.

Other types of cells

Although T cells are the primary targets of ICIs, various types of innate immune cells, such as macrophages, dendritic cells (DCs), and myeloid-derived suppressor cells (MDSCs), also play critical roles in the efficacies of different ICI therapies.[72] Myeloid cells express PD-1 and PDL-1.[73,74] Macrophages and DCs can stimulate $CD4^+$ T cells, present tumor antigens, and induce antitumor immune responses. Previous data showed that senescent macrophages expressed p16 and SA-β-gal, which are markers of cellular senescence.[75] The functions of DCs decrease with aging, including antigen presentation, phagocytosis, and IFN expression.[76,77] With aging, the phenotype of macrophages transforms from the M1(Classically activated macrophage) phenotype to the M2 (Alternatively activated macrophage) phenotype. The M1:M2 ratio is the key number for the immunosuppressive network because M2 could produce immunosuppressive cytokines inhibiting effector cells' function.[47] Senescent-associated macrophages (SAMs) may lead to T cell senescence and exhaustion through cytokine secretion.[15] SAMs secrete prostaglandin E2 (PGE2), an immunosuppressive cytokine, which upregulates PD-L1 in other myeloid cells and tumor cells by activating the cyclooxygenase 2 (COX-2)-microsomal prostaglandin E synthase 1 (mPGES1)-PGE2 pathway and the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, respectively.[15]

MDSCs, a subpopulation of neutrophils, are associated with tumorigenesis because they suppress T cell function and activation. Specifically, decreased CD62L expression in MDSCs can inhibit the expansion and activation of naïve T cells in the peripheral blood, as CD62L can enable naïve T cell migration to the lymph nodes.[78] MDSCs release reactive oxygen species, which induces T cell dysfunction, promotes Treg expansion, and enhances the expression of key proteins, such as Arginase 1, CD39/73, and IL-10.[79] Therefore, MDSCs can create a tumor-suppressive microenvironment that facilitates tumor formation and metastasis. Inflammaging, which is commonly observed in older individuals, may cause a shift in hematopoiesis from lymphopoiesis to myelopoiesis, resulting in the induction of an inflammatory environment. Both of these factors contribute to an increased number of MDSCs.[80] The results of many studies have shown that an increased frequency of circulating MDSCs and the TME are closely related to poor treatment outcomes and short OS in patients with various types of cancer.[81–83] Furthermore, the phenotypic and functional characteristics of MDSCs in older individuals are similar to those in younger individuals, indicating that even senescent

MDSCs can exhibit strong suppressive effects.[84] Thus, the increased number of MDSCs and their ability to maintain their suppressive capacity can create an environment that favors immune suppression, which can contribute to tumor development and induce immune resistance during ICI therapy.[85] Taken together, these findings indicate that increased numbers of MDSCs, Tregs, and macrophages form an age-related immunosuppressive network that influences the efficacies of different ICI therapies.[86]

Inflammaging, cancer, and immune checkpoint inhibitors

The close relationships between inflammation and cancer have long been appreciated.[87] Inflammation in the TME influences the tumor fate and efficacies of ICI therapies.[88,89] Inflammation is one of the seven pillars of senescence and is associated with many geriatric diseases.[90] Although inflammaging is typically characterized as a chronic, systemic, and low-grade state of inflammation,[8] the expression levels of anti-inflammatory cytokines (such as IL-10, IL-4, and IL-13) may also increase to affect the balance in the immune response.[91]

The mechanisms underlying inflammation are as follows: (1) the secretory ability of senescent cells is enhanced via nuclear factor-kappa B (NF-κB) activation, and senescent cells secrete growth factors, chemokines, inflammatory mediators, and other related cytokines, where this phenotype is referred to as the senescence-associated secretory phenotype (SASP).[92] Furthermore, p38 mitogen-activated protein kinase (MAPK) contributes to the SASP, mainly through transcriptional regulation of the *NF-κB* gene, which leads to the expression of pro-inflammatory genes.[93] Senescent cells produce cytokines that can induce an inflammatory state in the tissue microenvironment and affect surrounding cells through autocrine and paracrine signaling, which can accelerate the aging process;[92] (2) with age, the abundance of damage-associated molecular patterns (DAMPs) increases, which can activate innate immunity and stimulate immune cells to release pro-inflammatory mediators;[94] (3) autophagic and proteasomal activity declines with age due to the accumulation of misfolded proteins, which can trigger an inflammatory response.[95]

In summary, inflammation is characterized by dysregulation of the inflammatory state, resulting in an imbalance between pro-inflammatory and anti-inflammatory responses.[96] An inflammatory environment is related to an increased incidence of cancer,[97] and the increased frequency of senescent suppressive cells in the TME can secrete more inhibitory cytokines, which can promote cancer growth and development.[53,86] Furthermore, increased levels of inflammatory cytokines have been associated with poor responses to ICI treatments. For instance, inflammaging can lead to increased expression of pro-inflammatory mediators such as TNF-α, IL-6, and IL-1.[98] Previous data showed that TNF inhibition enhanced the antitumor effects of ICIs and reduced immune-related adverse events (irAEs).[99] Furthermore, researchers found that patients receiving a combination of ICIs and celecoxib had better treatment outcomes.[100] The underlying mechanism was that celecoxib reduced the levels of pro-inflammatory mediators such as IL-6 and IL-1β, leading to remodeling of the TME. Previous observations indicated that celecoxib enhances the function of $CD8^+$ effector T cells in the TME by inducing IL-2 and IFN-γ secretion and OX40 and CD137 expression.[100] Inflammation generates an abnormal inflammatory environment, which can contribute to tumorigenesis and tumor development, while also reducing the efficacies of different ICI therapies.

Immune-related adverse events in older people

Although ICIs can inhibit tumor growth, the accompanying side effects, known as irAEs, can impact the efficacy and performance of ICIs.[101] IrAEs can affect multiple organs including the skin, lungs, and heart.[102] Recent findings have suggested that the incidence of irAEs strongly correlates with advanced age. The results of one study showed that older patients (aged ≥70 years) with cancer who were treated with ICIs were more prone to irAEs than younger patients (aged <70 years).[103] Similarly, in a phase I immunotherapy trial, the frequencies of grade I–II irAEs were much higher in older patients treated with ICIs than in younger patients.[104] The possible mechanisms underlying this age-related increase in irAEs require further investigation. Researchers have suggested that pre-existing autoimmune diseases may be associated with irAEs during ICI therapy and patients treated with immunosuppressive drugs at the beginning of ICI therapy may be less prone to irAEs.[102] Immunosenescence and inflammation can induce autoimmune diseases and increase pro-inflammatory cytokine levels.[4] Therefore, a dysfunctional immune response and pro-inflammatory status in older individuals may contribute to their increased susceptibility to irAEs.

This article reviews recent developments in the fields of ICIs and immunosenescence. Although there is no direct evidence proving the impact of immunosenescence on ICIs, attention should be paid to the efficacies of different ICI treatments in older patients. Additionally, data collection was not comprehensive as it was based solely on the knowledge of the authors.

Conclusion and future directions

ICIs can be effective in treating various types of cancer; however, their efficacy and safety in older individuals remain unclear. The studies compiled in this review demonstrate that both immunosenescence and inflammaging can lead to a decline in their ability to mount an antitumor response and an increased risk of irAEs in older individuals treated with ICIs. These age-related changes can alter the function and number of immune cells and increase the levels of inflammatory cytokines, resulting in a dysfunctional immune response and an unbalanced inflammatory status.

Predicting and improving the performance of ICIs in older individuals is an important area for future research. Previous findings have suggested that the percentage of SIP^+ T cells and circulating pro-inflammatory cytokine levels may be useful predictors of ICI efficacy in older individuals.[11,99,105,106] Our future aim is to establish a scoring system to evaluate the degree of immunosenescence and inflammation. This will help enhance the effectiveness of ICIs therapy while minimizing adverse events.

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Authors contribution

Chuandong Hou: Data curation, Writing – original draft preparation; Zining Wang: Writing – review and editing; Xuechun Lu: Writing – review and editing, funding acquisition.

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None.

Data availability statement

All data are available within this manuscript.

Conflict of interest

None.

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