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REVIEW

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Immunosenescence and cancer: molecular hallmarks, tumor microenvironment remodeling, and age-specific immunotherapy challenges

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Abstract

Immunosenescence, the age-related decline in immune function, profoundly impacts cancer progression and therapeutic outcomes by fostering a tumor-promoting microenvironment and impairing immune surveillance. This review delineates eleven molecular hallmarks of immunosenescence, including genomic instability, telomere attrition, epigenetic dysregulation, mitochondrial dysfunction, and chronic inflammation, which collectively drive immune cell dysfunction and systemic immunosuppression. Aging reshapes the tumor microenvironment (TME) through recruitment of immunosuppressive cells, senescence-associated secretory phenotypes (SASP), and metabolic reprogramming, contributing to therapy resistance and poor prognosis in elderly patients. While immunotherapies such as immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T-cell immunotherapy (CAR-T) cells show promise, their efficacy in aging populations is limited by T cell exhaustion, myeloid bias, and altered intercellular communication. Emerging strategies—including senolytics, epigenetic modulators (e.g., histone deacetylase (HDAC) inhibitor), and metabolic interventions (e.g., spermidine, nicotinamide mononucleotide (NMN))—highlight potential avenues to rejuvenate aged immunity. Single-cell multi-omics (single cell RNA-seq, single cell ATAC-seq) further unravel immune cell heterogeneity, revealing tissue-specific chromatin accessibility dynamics and novel targets like interleukin-34 (IL-34) for microglia-mediated neuroinflammation. However, challenges persist in translating preclinical findings to clinical practice, necessitating age-tailored trials and biomarker-driven approaches. By integrating mechanistic insights with translational innovations, this review

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underscores the urgency of addressing immunosenescence to optimize cancer immunotherapy for aging populations, ultimately bridging the gap between aging biology and precision oncology.

Introduction

Aging is an inevitable biological process causing profound physiological alterations, particularly in the immune system [1, 2]. Immunosenescence, defined as the progressive decline in immune function with age, increases susceptibility to infections, chronic inflammation, and cancer development in older adults [3, 4]. Changes in bone marrow hematopoietic function, together with thymic atrophy, cause an imbalance in the distribution of immune cell subpopulations [5]. In addition, immune cells themselves undergo various metabolic disorders, including mitochondrial dysfunction and disruption of energy metabolism pathways [6, 7]. These factors together lead to the secretion of pro-inflammatory factors by immune cells, causing chronic low-grade inflammation and inflammaging, which is a characteristic of immune aging [8]. Here, to better study and observe the phenomenon of immunosenescence, we propose three criteria for a marker that can be used to determine immunosenescence: (1) manifestation during aging; (2) causal acceleration of immune dysfunction when exacerbated; (3) potential for reversal through targeted interventions (essential for "core drivers"). Some correlates are integral to the process but classified as "contributing factors" due to insufficient direct intervention evidence. Based on these criteria, we identified 11 phenomena that mark immunosenescence: telomere attrition, epigenetic alterations, disabled autophagy, mitochondrial dysfunction, cellular senescence, hematopoietic stem cells (HSCs) myeloid bias, altered intercellular communication, chronic inflammation as "core drivers", and genomic instability, loss of proteostasis, gut dysbiosis as 'contributing factors'. When identifying these hallmarks, we also take the character of immunosenescence into consideration. Take an instance, though people are likely to regard stem cell exhaustion as one of the aging hallmarks, we think that in immunosenescence, HSC myeloid bias could describe aging driven by stem cell abnormalities better. However, it is important to note that these markers aren't completely independent, but are interconnected. Collectively, these markers synergize to drive a systemic state of immunosenescence, characterized by impaired immune surveillance, reduced cytotoxic responses, and increased chronic inflammation which profoundly influences cancer occurrence, progression, and resistance to therapies [9].

As data shows, cancer incidence markedly increases with age, making it a prominent health issue in elderly populations, creating urgent needs to understand aging-cancer interactions in aging global population [10, 11]. Emerging evidence indicates that immunosenescence critically influences cancer progression and treatment response by shaping tumor-promoting microenvironments [12]. The tumor microenvironment (TME) is a dynamic environment comprising fibroblasts, vascular endothelial cells, immune cells, and non-cellular factors, including cytokines and the extracellular matrix (ECM) [13]. The aging TME can both promote and inhibit immune responses, depending on the regulatory networks and cellular interactions [14]. Most of the time, aging-induced changes within the TME, including elevated pro-inflammatory cytokines and the recruitment of immunosuppressive cells, are shown to accelerate immunosenescence and promote tumor growth [15]. However, situations may be different in various types of tumors [16].

Besides, aging-associated alterations in systemic immunity impair tumor recognition and clearance, influencing tumor development and metastasis, finally resulting in poorer prognosis and increased treatment resistance in elderly patients [17].

Tumor immunotherapy is a therapeutic method that enables the body to generate tumor-specific immune responses through active or passive means, and exerts its function of suppressing and killing tumor cells, which mainly includes molecular targeted therapy, immune checkpoint inhibitors [18], adoptive cell transfer (ACT) (such as dendritic cell (DC) vaccine, CAR-T cell therapy, CAR-natural killer (NK) cell therapy, tumor infiltrating lymphocytes (TILs) cell therapy and cytokine-induced killer (CIK) cell therapy) [19], cytokine therapy and tumor vaccines [20]. Nevertheless, with the alterations both in systemic immunity and TME as aging among tumor patients, the immunotherapy efficacies differ between young and aging populations with cancer [21]. Understanding these mechanisms is crucial as most cancer patients requiring treatment are elderly.

In short, this review aims to define key molecular and cellular features of immunosenescence based on a proposed framework and highlight the mechanistic role of immunosenescence in modulating cancer development, progression, and treatment response both systematically and locally. It further explores age-specific immune remodeling in the TME and discusses emerging strategies to overcome immunosenescence in cancer patients.

Hallmarks of Immunosenescence

Genomic instability

Many studies have shown the relationship between aging and genomic instability, and the same applies to

immunosenescence. Genomic instability biomarkers, such as micronucleus (MNs) and centromere positive micronuclei (MNC+), have been reported in leukocytes [22]. The accumulation of DNA damage with aging, which is frequently caused by deficiencies in the DNA repair mechanism, such as the double-strand break (DSB) repair and mismatch repair results in the genomic instability in aging immune cells [23, 24]. In vitro experiments have demonstrated that the dysregulation of mismatch repair system genes, especially the reduction of MutL heterodimers in elderly cloned T cells, results in microsatellite instability (MSI) [24, 25]. For example, T cells, under age-related oxidative stress, experience mitochondrial DNA (mtDNA) translocation into the nucleus and integration near the telomeres, generating genetic alterations and elevated MNs with diminished proliferation [26]. Notably, macrophage-specific aging marker CD63 is upregulated in the absence of LaminA/C, leading to nucleotide excision repair (NER) and DNA damage, although mechanistic details remain elusive [27].

Transposons, as elements that affect gene expression and function, also mediate genomic instability in the leucocytes of aging organisms. Long interspersed elements-1 (LINE1) hypomethylation and ALU-J/sx destabilization are both involved in this process [22, 28]. Interestingly, LINE1 hypomethylation exhibits no significant correlation with MNC + levels, which potentially attributes to the small sample size; and regional differences are exhibited in LINE1 hypomethylation as aging [22, 29].

Telomere attrition

Telomere attrition, characterized by progressive shortening and reduced telomerase activity, exists in immunosenescence [30, 31]. Currently, leukocyte telomere length (LTL), measured via quantitative polymerase chain reaction (qPCR), flow-fluorescence in situ hybridization (flow-FISH) and terminal restriction fragment (TRF), is one of the key biological markers investigated in the field of aging research as a potential indicator of cellular senescence and overall biological age [32–34]. It should be noted that chronological aging does not always parallel biological aging, for example, more rapid LTL attrition may predict cognitive aging in healthy young adults. However, telomere attrition in the elderly is often faster than in younger individuals [35–37]. Currently, some biomarkers such as FetuinA [38] and certain metabolites [39] have been found to indirectly predict LTL. Through diverse detection techniques, an increasing number of factors have been shown to accelerate LTL shortening. Infectious pathogens (human immunodeficiency virus (HIV) [40], cytomegalovirus (CMV) [41], herpes simplex virus type 1 and human herpesvirus 6 [41]) are all independently associated with LTL attrition. HIV induces telomere attrition through inhibition of telomeric repeat binding factor 2 (TRF2), telomerase, topoisomerase I and II alpha (Top1/2a), and ataxia telangiectasia mutated (ATM) kinase activities, resulting in the accumulation of dysfunctional telomere-induced foci (TIF), the DNA damage marker γ H2A family member X (γH2AX), and topoisomerase cleavage complex (TOPcc), ultimately leading to telomere attrition and T cell senescence. However, since this experiment was conducted using an arsenic compound KML001 to artificially reproduce a process similar to HIV-induced CD4 + T cell senescence, the result requires in vivo validation [42]. Besides, While combination antiretroviral therapy (cART) has the potential to ameliorate the condition of HIV-infected patients, it concomitantly accelerates microglial aging by inhibiting telomerase activity and upregulating TRF-1, thereby increasing IL-1β expression and promoting neuroinflammation and HIV-associated neurocognitive disorders (HAND) [43].

Lifestyle [44–47], and other pathophysiological factors [48–57] can also lead to LTL shortening. Notably, the impact of specific factors exhibits gender disparities: high-intensity physical activity predominantly shortens telomeres in elderly women [53], while hostility primarily affects elderly men [55]. Paradoxically, cross-sectional data indicate that physical activity (PA) and physical fitness (PF) mitigate age-related telomere attrition regardless of gender [58], suggesting intensity-dependent effects. Although dialysis also accelerates telomere attrition, it also leads to compensatory increases in leucocyte telomere length, which may be related to the increase in peripheral immature leucocytes to replenish depleted ones [54].

Contradictory findings exist for other factors. Most studies believe that obesity accelerates telomere attrition [47, 59], and TRF1 upregulation mediates this process [60], but a longitudinal analyse shows no consistent association in the British Birth cohort [61], indicating that obesity may be a factor with regional differences. The impact of chronic psychosocial stress on telomere attrition has also shown contradictory results in different studies, possibly due to the heterogeneous study designs and the complex nature of chronic psychosocial stress from individual and environmental composition, including social connections, health-maintaining behaviors, and psychological resources [62, 63]. Besides, cortisol may be involved in the accelerating telomere attrition through neuroendocrine mechanisms [54].

In addition, LTL shortening is also associated with many age-related diseases [64–68]. Interestingly, a meta-analysis indicated that short LTL associated with biological aging rather than chronological age can serve as a predictor for myocardial infarction, but another study showed that this correlation only appeared in men [64,

69]. Fortunately, TA-65, a type of telomerase activator, could reverse immunosenescence in acute coronary syndrome (TACTIC) [70], indicating a possibility in the treatment of myocardial infarction. This suggests that attention should be paid to biological aging and potential risks of age-related diseases even in young people. Although LTL shortening is associated with atherosclerosis, one study showed that this association diminishes after adjustment for age [71]. When further exploring the molecular mechanisms of telomere attrition, in addition to leucocytes, it has been found that hematopoietic stem cells (HSC) in the elderly also have defects in telomerase and telomere length attrition, which may be inherited by descendant cells, leading to poorer hematopoietic potential and lower immune capacity in the elderly [72].

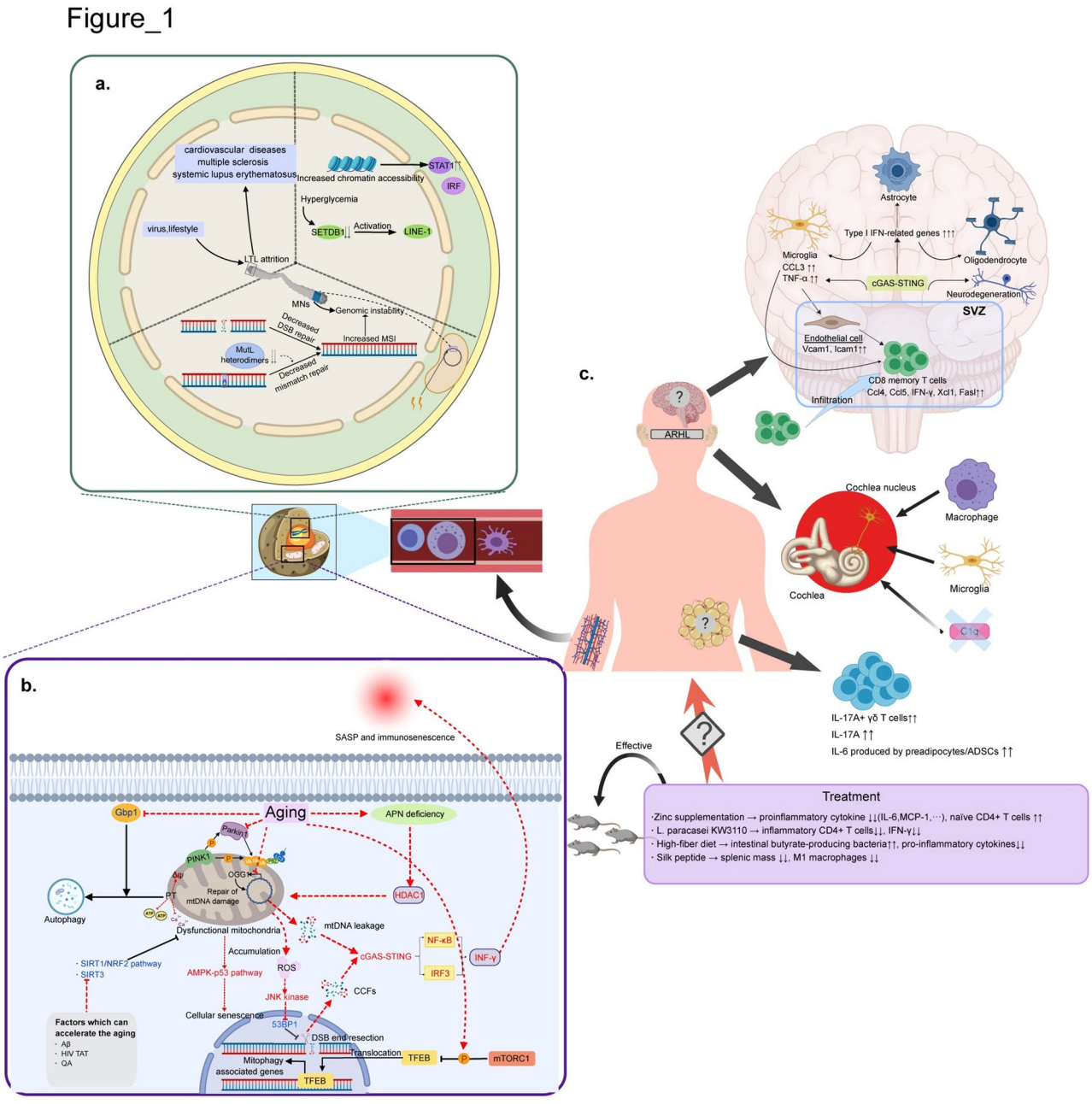
Epigenetic alterations

Epigenetic alterations often vary with biological aging. Epigenetic clock initially predicted biological age by analyzing methylation patterns at 353 CpG sites [73]. It utilizes not only cells in heterogeneous tissues, but also individual cell types, including neutrophils, monocytes, CD4 T cells and immortalized B cells as the marker to predict biological aging [73–76]. However, previous versions (Hannum clock [77], Horvath clock [73], Horvath Skin and Blood clock [78], and PhenoAge [79]) are often confounded by age-related shifts in immune cell composition, especially CD8 + T cell differentiation states within PBMCs. The novel IntrinClock overcomes this limitation by using CpG sites stable during CD8 + T cell differentiation, enabling consistent and more accurate biological age prediction across immune subsets [75, 80]. Changes in chronic inflammation are also linked to these epigenetic shifts. Below, we will provide an overview of these studies. However, limitations persist in linking global epigenetic alterations to immune cell phenotypic changes and functional decline.

Individuals in old age often experience a chronic, low-grade inflammatory state, which is also a characteristic of immunosenescence. Epigenetic abnormalities can cause and accelerate immunosenescence through both systemic and tissue-specific mechanisms. Systemically, ATAC-seq showed transition of CD8 + T cells to age-associated granzyme K (GZMK)-expressing CD8 + T (Taa) cells is regulated by the T-box family transcription factor eomesodermin (EOMES). Taa cells expand in both aged humans and mice, upregulating CD49d and acquiring efficient tissue homing capacity, which, together with their secretion of GZMK, may contribute to systemic inflammation [81]. Furthermore, age-related decrease of microRNA (miR)-17-92a in naïve-CD8 + T cells contributes to their reduction of quantity [82]. Additionally, a deficiency in miR-181a, whose target is SIRT1, has been shown to impact T cell function, leading to excessive replication stress and inflammatory cytokines in naive T cells from older individuals and miR-181ab1-deficient murine T cells. This replication stress is linked to reduced histone expression and delayed cell cycle progression, primarily due to the repression of histone gene transcription by SIRT1 by binding to the promoters and reducing histone acetylation. Furthermore, treatment with SIRT1 inhibitors decreases the secretion of inflammatory cytokines in mice with miR-181a-deficient T cells [83]. Besides, decreased expression of H2AX in CD8 + CD28- T cells, which are a subset related to aging, leads to less targets for miR-24, resulting in a decreased potential to activate the DDR response [84]. This, as we mentioned above, increases genome instability and causes immunosenescence. Finally, the contribution of chromatin remodeling to immunosenescence can't be ignored. The large-scale chromatin reorganization distinguishes young and old bone marrow progenitor (pro-) B cells, which causes reduced interactions within topologically associated domains (TADs) with aging. Reduced TADs, containing genes important for B cell development, impair B lymphopoiesis [85].

Concurrently, tissue-localized epigenetic dysregulation fuels immunosenescence by inflammation. The downregulation of SET domain-bifurcated histone lysine methyltransferase 1 (SETDB1) induced by hyperglycemia activates the LINE-1 promoter, triggering the aging phenotype of macrophages and driving periodontal immunosenescence. This process can be reversed by metformin in preclinical models [72]. Aging intestinal stem cells in mice exhibit increased accessibility of inflammation-related loci on chromosomes due to chromatin remodeling, thus exacerbating gut inflammation, although the specific molecular mechanisms require further study [86]. Furthermore, interferons and their related signaling pathways play crucial roles in the inflammatory network, with abnormally high expression of transcription factors signal transducer and activator of transcription 1 (STAT1) and interferon regulatory factors (IRFs) found in elderly individuals [87]. Subsequent research suggests that the abnormal expression of these transcription factors in the liver and kidneys of aged mice may be associated with a general open chromatin rearrangement related to aging, and dietary restriction (DR) can partially rescue the inflammatory environment by decreasing the chromatin accessibility of STAT1 and IRF regions [88]. This discovery provides a non-invasive and relatively harmless therapeutic approach to alleviate chronic inflammation in aging individuals.

Besides, inflammation reciprocally accelerates epigenetic aging, establishing a vicious cycle. Studies on human skin have shown that exposure to light can induce epidermal inflammation, thus promoting epigenetic aging characterized by methylation changes, which can persist



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for decades. However, it seems that not all photoexposed skin areas exhibit this phenomenon, and the reason for this variability remain unclear [89]. Infection can also accelerate epigenetic aging, although whether this effect is related to inflammation is yet to be determined. Hepatitis C virus (HCV) infection was found to correlate with epigenetic age acceleration (EAA), with the most pronounced in patients who developed hepatocellular carcinoma (HCC) after sustained virologic response (SVR), and this acceleration can be reversed by direct-acting antivirals (DAAs). Nevertheless, since this result was derived from the Horvath clock detecting DNA methylation in peripheral blood mononuclear cells (PBMCs) rather than liver cells, it cannot be determined whether the accelerated epigenetic aging in patients is directly caused by HCV or indirectly triggered by chronic inflammation [90]. One study suggested that infections leading to EAA are associated with exposure to susceptible environments and past infections rather than recent infections. A study comparing epigenetic aging in individuals from leprosy-endemic and non-endemic areas in Brazil found no difference in aging speed between infected and

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Fig. 1 A focus on the core molecular mechanisms of immune senescence and chronic inflammatory networks. (**a**) Some factors (virus, unhealthy lifestyle) will lead to LTL attrition, which will cause some age-related diseases. SETDB1 downregulation caused by elevated glucose levels activates the LINE-1 promoter in macrophages, triggering an aging phenotype in immune cells. Furthermore, a general open chromatin rearrangement related to aging results in abnormally high expression of STAT1 and IRFs, finally leading to the activation of IFNs and their related signaling pathways. Genomic instability derived from many factors; MNs are one of them. The production of them is due to the mitochondrial DNA (mtDNA) translocation into the nucleus and integration near the telomeres. Besides, the reduced MutL heterodimers can lead to decreased efficiency of mismatch repair, resulting in MSI, and as well as the efficiency of double-strand break (DSB) repair. (**b**) Mitochondrial dysfunction primarily interferes with cellular homeostasis through various pathways, including abnormalities in mitochondrial membrane potential, increased ROS production, and mtDNA leakage. The proinflammatory signal is presented in red, while anti-inflammatory is in blue in the figure. These factors contribute to inflammation through the activation of the cGAS/STING pathway, activating the downstream molecules such as NF-κB and IRF-3. Suppressing mitochondrial autophagy and accumulating mtDNA damage are regulated by reducing the mTOR/TFEB signaling pathway, the mtOGG1 expression, and the PINK1/Parkin-mediated polyubiquitination of mitochondria. Moreover, ROS can promote inflammation by activating downstream signaling pathways, such as JNK kinase, through mitochondria-to-nucleus retrograde signaling. This process will then inhibit the negative regulation of 53BP1 on DSB end resection, leading to the release of CCFs and the activation of the downstream pathway. Furthermore, Guanylate binding protein 1 (Gbp1), under normal conditions, eliminates inflammation-induced dysfunctional mitochondria via the mitochondrial autophagy pathway (black line). In aging macrophages, Gbp1 expression is downregulated, leading to mitochondrial dysfunction (red line). This dysfunction activates the AMPK-p53 pathway, inducing cellular senescence and promoting an inflammatory response through the secretion of SASP (senescence-associated secretory phenotype) factors. Besides, APN deficiency leads to a significant increase in HDAC1, exacerbating mitochondrial damage. Several pathological factors can also exacerbate mitochondrial dysfunction in aging immune cells, such as Aβ, HIV TAT and QA. They can inhibit the SIRT1/NRF2 and SIRT3 pathway. (**c**) Mild chronic inflammation is considered a hallmark of aging and a core driving factor for age-related damage and diseases. In aging brains, the activation of the cGAS-STING signaling pathway leads to increased expression of type I IFN-related genes in many types of cells, finally increasing the inflammatory cytokines. Additionally, TNF-α, also induced by the activation of the microglial cGAS-STING pathway, drives neurodegeneration and activates the expression of adhesion molecules Vcam1 and Icam1 in brain venous endothelial cells in the aged subventricular zone (SVZ), finally promoting T cell infiltration. Furthermore, aged microglia secrets CCL3 to recruit peripheral CD8 memory T cells infiltrating the brain microenvironment. CD8 memory T cells then release SASP. However, how these molecule changes are associated with functional alteration in aging brain remain unclear. Chronic inflammation in the cochlea and cochlear nucleus (CN) is caused by macrophages, microglia and C1q deposition, ultimately in coordination to the development of age-related hearing loss (ARHL). Furthermore, the quantity of tissue-resident memory γδ T cells (CD44hi62LlowCD69+) increase in the visceral adipose tissue (VAT) of aging individuals. These γδ T cells promote low-grade chronic inflammation in adipose tissue by upregulating IL-17 A, which mediates the production of IL-6 produced by preadipocytes/adipose-derived stem cells(ADSCs). Finally, animal studies have found that dietary strategies are a feasible approach to improve age-related chronic inflammation, but the safety and effectiveness in human need further research

uninfected subjects within endemic areas, but significant EAA was observed in individuals from endemic areas compared to those from non-endemic areas [91]. These results all imply chronic inflammation's enduring impact on epigenetic aging. Moreover, epigenetic age acceleration caused by both HCV and leprosy infection exists regional differences [90–92].

Epigenetic biomarkers show promise for clinical assessment of inflammation status and immunosenescence in elderly individuals. Notably, the epigenetic inflammation score (EIS) based on CpGs outperform conventional C-reactive protein (CRP) in assessing low-grade inflammation in elderly individuals [93]. Besides, the measurement of DNA methylation (DNAm) in peripheral blood cells has been used to predict immune cell infiltration in Alzheimer's disease and atherosclerosis [94]. These studies reveal the potential of epigenetic changes in clinical applications.

Although in most cases, epigenetic changes related to aging and inflammation follow predicted patterns, such as methylation of promoter regions leading to gene downregulation and acetylation leading to gene upregulation, recent research has identified some exceptions [95, 96]. In the elderly, hypomethylation of the inflammation-related gene C-X-C Motif Chemokine Ligand 10 (CXCL10) increases its expression but paradoxically correlates with enhanced spatial memory in carriers of the single nucleotide polymorphism (SNP) rs56061981 in CXCL10, which eliminates the CpG-136 site and increases the gene activity [97]. This seemingly contradictory result requires further validation with larger sample size. Similarly, inflammatory-related genes which upregulate in the brain with aging (Age-up genes) show reduced histone H3 acetylated lysine 27 (H3K27ac), a histone mark typically associated with activation, and HDAC inhibitors (HDACi) suppress the expression of Age-up genes [98]. These results, combined with previous findings, indicate that the regulatory role of H3K27ac in the inflammatory environment of aging individuals is tissue-specific [96, 98]. Besides, HDACi also show therapeutic potential in prevention of CAR-T cells exhaustion by enhanced expression of transcription factors TCF4 and LEF1, thereby activating the Wnt/β-catenin signaling [99]. Figure 1a shows the molecule mechanism of how genomic instability, telomere attrition and epigenetic alterations lead to immunosnescence. Collectively, epigenetic alterations represent a fundamental mechanism driving chronic inflammation in immunosenescence. Furthermore, these anomalies underscore persistent challenges: immune cell heterogeneity confounding epigenetic assays, the unclear causal mechanism between specific epigenetic modifications and immune decline, and the contradictory tissue specificity of inflammation-driven epigenetic aging. In the future, it will be

necessary to combine single-cell epigenomics to resolve immune cell subpopulation dynamics, target reversal of epigenetic-immune imbalances through interventional experiments, and explore the long-term effects of episodic memory on immunosenescence in the context of infections/environmental exposures. Beyond epigenetic changes, loss of protein homeostasis also emerges as a critical hallmark of immunosenescence, for impaired proteostasis contributes significantly to functional decline in the antigen presentation.

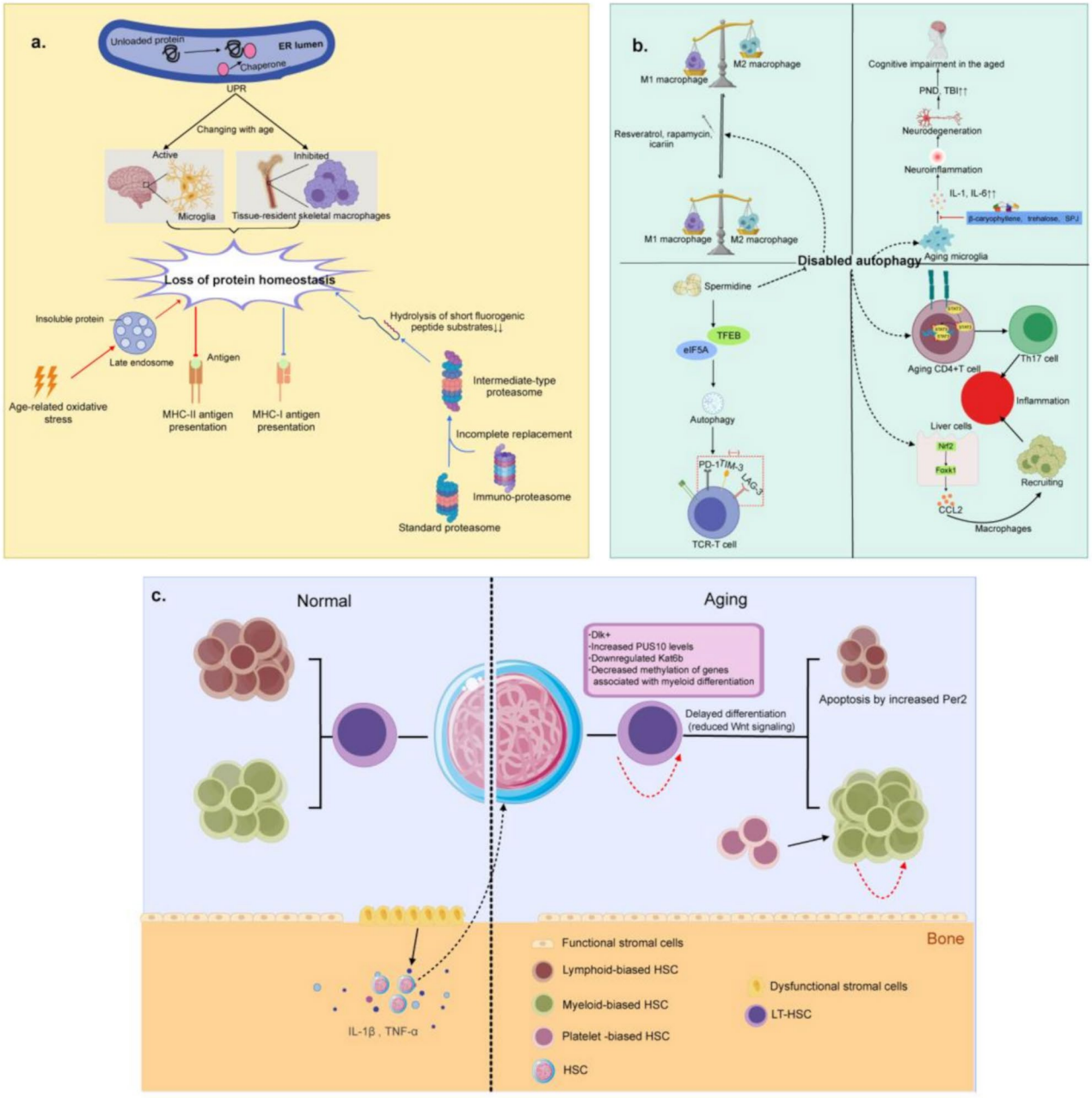
Loss of proteostasis

Proteostasis usually means the balanced state of processes such as protein synthesis, folding, repair, degradation, and renewal within cells [100]. Upon aging, proteostasis can be disrupted by many factors. Currently, discussions of impaired proteostasis in immunosenescence mainly revolve around the disabled autophagy and the dysregulated unfolded protein response (UPR) in macrophages and microglia. In macrophages, age-related autophagy reduction promotes pro-inflammatory M1 polarization [101]. Resveratrol stimulation significantly restores autophagic flux by increasing the number of autophagosomes in senescent macrophages (S-MΦs), reducing reactive oxygen species (ROS), thus promoting the M1-to-M2 transition [102]. Similarly, improvement in autophagy leading to the anti-inflammatory polarization of S-MΦs has also been observed with rapamycin treatment, which has been found to promote the degradation and myogenesis of vascular graft poly glycerol sebacate-polycaprolactone (PGS-PCL), a synthetic vascular graft material that can utilize the host's regenerative capacity to transform in situ into a blood vessel-like structure, thereby improving vascular remodeling in aged rats [103]. Despite the macrophages in the peripheral environment in the aged, treatment targeting the autophagic defect in S-MΦs of the hematopoietic microenvironment is also under development. Icariin restores osteogenesis of senescent bone marrow mesenchymal stem cells (S-BMSCs) by activating autophagy in S-MΦs, suppressing SASP-mediated inflammation [104].

Microglia, a type of resident mononuclear macrophages in the central nervous system [105], also exhibit age-dependent autophagy impairment, which exacerbates neuroinflammation and cognitive decline. Perioperative neurocognitive disorders (PND), associated with neuroinflammation mediated by microglia with decreased autophagy, are cognitive impairments caused by surgery and anesthesia, with a higher incidence in elderly patients [106]. β-caryophyllene (BCP), a natural terpene that specifically activates CB2 receptors (CB2R), can inhibit the release of IL-1 (interleukin-1) and IL-6 inflammatory cytokines from microglia in the hippocampus and restore their autophagic capacity in aging mice [107]. Similarly, older patients with traumatic brain injury (TBI) have a higher mortality rate and worse prognosis than younger patients. This can be attributed to the decline in autophagy, the elevation of phagocytosis, the inflammatory phenotype and oxidative stress that occurs in microglia under the influence of ageing, which are further exacerbated by TBI, potentially aggravating neurodegeneration and a more serious neuroinflammation. Surprisingly, an enhancer of autophagy, trehalose, may inhibit microglia phagocytosis by acting upstream of the autophagy pathway, finally restoring motor and cognitive functions in aged TBI mice [108]. Notably, a microglial subset, autophagy-dependent age-acquired microglia (ADAM), emerges via IL-34- colony stimulating factor 1 receptor (CSF1R) - extracellular regulated protein kinases (ERK)/ (adenosine 5'-monophosphate-activated protein kinase) AMPK signaling, limiting neuroinflammation. Nevertheless, this subset decreases when aging. Fortunately, IL-34 supplementation expands this, suggesting therapeutic potential for neurodegenerative diseases [109]. In the future, it will be essential to ascertain the potential reduction of the ADAM subset in age-related neurodegenerative diseases.

While much attention has been focused on autophagy, loss of proteostasis in aging also involves complex alterations in UPR signaling within those myeloid cells. In aging individuals, UPR displays varying expression changes in immune cells across different tissues, ultimately leading to the loss of protein homeostasis. Microglia cells in aging rats exhibit abnormal or overactive UPR, which impairs protein homeostasis. NT-020, a blend of polyphenols, has been shown to inhibit UPR signaling [110]. However, its causal role in microglial aging remains unclear. Conversely, tissue-resident macrophages in aged mice recovering from influenza A virus-induced pneumonia show upregulated proteostatic stress genes but downregulated UPR components [111]. These contradictory UPR expressions may stem from species-specific differences, tissue variability, or latent viral effects, necessitating further mechanistic studies across standardized models. Additionally, investigation into the immune functional alterations caused by protein homeostasis loss in aging individuals necessitates further exploration.

Age-related proteostatic failure directly impairs immune function by interfering with antigen presentation processes. In dendritic cells, oxidative stress induces protein damage (carbonylation, glycation, lipoxidation), forming insoluble aggregates in late endosomes that disrupt major histocompatibility complex (MHC) class II antigen presentation and endosomal proteostasis [112]. Proteasomes consist of immuno-proteasomes and standard proteasomes, each composed of different subunits. Aged mouse hepatocytes exhibit altered proteasome



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composition, with incomplete replacement of standard subunits by immuno-subunits, forming intermediate-type proteasomes. This shift correlates with reduced hydrolytic activity and may compromise MHC I antigen peptide generation, linking proteostatic decline to adaptive immune dysfunction [113, 114].

Disabled autophagy

Autophagy plays a crucial role in modulating the function of immune cells, influencing their inflammatory phenotype and immune responses. In addition to myeloid cells mentioned above, aging also impairs autophagy in lymphocytes, notably in T cells, compromising their maintenance, functionality, and immunotherapeutic responsiveness. A prominent feature of aged $CD8^+$ T cells is the decline in autophagic activity, which undermines the maintenance of memory T cells and diminishes vaccine efficacy. This deterioration is mechanistically linked to spermidine biosynthesis decline, for the spermidine maintains T cell autophagy through the translation factor eukaryotic translation initiation factor 5 A (eIF5A) and the transcription factor EB (TFEB) usually [115–117].

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Fig. 2 Association of protein homeostasis imbalance with immune cell dysfunction. (**a**) In aging individuals, UPR displays varying expression changes in immune cells across different tissues (such as microglia cells and tissue-resident skeletal macrophages), ultimately leading to the loss of protein homeostasis. Age-related oxidative stress increases oxidatively damaged proteins, causing the formation of insoluble protein aggregates in late endosomes, which disrupts endosomal proteostasis and impairs the ability to mount an MHC class II-restricted immune response. Proteasomes consist of immunoproteasomes and standard proteasomes, each composed of different subunits. Intermediate-type proteasomes result from an incomplete replacement of standard subunits by immuno-subunits. This alteration contributes to the decreased hydrolytic activity of short fluorogenic peptide substrates, potentially accounting for the efficiency of MHC I antigen peptide generation. (**b**) Aging macrophages exhibit low levels of autophagy, which is a reason for their commonly observed M1 pro-inflammatory phenotype. Resveratrol, rapamycin and icariin treatment significantly reverse this phenomenon. Decrease in autophagy of microglia is associated with cognitive impairment by causing or aggravating the neuroinflammation and neurodegeneration, which induce a higher incidence of PND and TBI in older patients. BCP, trehalose and SPJ can inhibit the inflammation from microglia. Spermidine maintains T cell autophagy through the translation factor eIF5A and the transcription factor TFEB, while aging inhibits spermidine biosynthesis in T cells, thus increasing the expression of inhibitory immunoreceptors (PD-1, TIM-3 or LAG-3). Age-related autophagy decline in CD4 + cells of elderly subjects drives a Th17 profile by activating the Th17 master regulator, STAT3. Autophagy deficiency in liver cells triggers the senescence of liver cells and a SASP primarily consisting of chemokine CCL2, which is regulated by NRF2-dependent activation of Foxk1, recruiting F4/80 + or CD11b + macrophages to produce inflammation. (**c**) As individuals age, the capacity of hematopoietic stem cells (HSCs) to differentiate into various blood cell lineages exhibits differences, characterized by increased myeloid differentiation and decreased lymphoid differentiation. Aging HSCs exhibit delayed differentiation which occurs before the point that splits lymphoid fate from myeloid fate due to reduced Wnt signaling. It was found that increased Dlk1 expression, reduced ubiquitination of PUS10, downregulated Kat6b, decreased methylation of genes associated with myeloid differentiation is associated with myeloid bias. Furthermore, myeloid biased HSCs exhibit a significantly greater enhancement in self-renewal compared to those lymphoid biased. Besides, Period circadian clock 2 (Per2) induces apoptosis through phosphorylation of p53, and its expression increases in lymphoid biased HSCs in aging mice rather than myeloid biased HSCs. The proportion of HSCs with platelet bias increases in aged mice, and interestingly, these stem cells can also increase myeloid output. The occurrence of myeloid bias may also be related to changes in the aging bone marrow niche. Increased levels of IL-1β and TNF-α in the aging marrow niche promote myeloid biased differentiation and inflammatory. IL-1β is produced by dysfunctional stromal cells, leading to the occurrence of chronic, low-grade inflammation

Spermidine supplementation also rescues the antitumor activity of T-cell receptor-engineered T cells (TCR-Ts) by enhancing the proliferation and effector function and reducing inhibitory immunoreceptors expression (programmed death-1 (PD-1), T cell immunoglobulin domain and mucin domain-3 (TIM-3) or lymphocyte activation gene-3 (LAG-3)) caused by impaired autophagy [118].

Beyond $CD8^+$ T cells, autophagy impairment in aging $CD4^+$ T cells contributes to immune dysfunction by promoting a pro-inflammatory phenotype. Autophagy deficiency drives Th17 polarization via signal transducer and activator of transcription 3 (STAT3) activation, fueling chronic inflammation, and this process is reversible by metformin [119].

Surprisingly, declined autophagy in the aging process can also impact the immune response via non-immune tissue cells. Autophagy deficiency in liver cells triggers the cellular senescence and a SASP primarily consisting of C C motif ligand 2 (CCL2), which is regulated by nuclear respiratory factor 2 (NRF2)-dependent activation of forkhead box K1 (Foxk1), finally recruiting F4/80 + or CD11b + macrophages to indirectly produce inflammation. Deletion of C C motif receptor (Ccr2) significantly inhibits the accumulation of inflammatory cells in liver tissue [120].

In short, how loss of proteostasis and disabled autophagy relate to immunosenescence is described in Fig. 2a and b.

Mitochondrial defects

Mitochondria are crucial "energy factories", determining the energy metabolism and physiological status of immune cells. For instance, mitochondrial metabolic reprogramming in CD4 + T cells is essential for their subsequent differentiation into specific subsets [121]. Overall, aging leads to impairments in both mitochondrial quality and function in immune cells, which promotes an inflammatory phenotype in these cells and further accelerates the immunosenescence, and some details are presented in Fig. 1b.

The decreased mitochondrial mass plays a central role in driving immunosenescence through mitochondria's progressive dysfunction. The senescent T cell population (EMRA; effector memory CD45RA re-expressing T cells), which accumulates with aging, exhibits reduced mitochondrial mass [122, 123]. Interestingly, CD8 + EMRA cells show accelerated aging compared to CD4 + EMRA cells, also likely due to their lower mitochondrial mass, which leads to metabolic dysfunction [124]. Despite these changes, the transfer of functional mitochondria into CD4 + EMRA T cells restores mitochondrial function and aerobic metabolism, reducing ROS and enhancing infection control in vitro [125]. In contrast, aging memory $CD4^+$ T cells exhibit a paradoxical increase in mitochondrial mass. This elevation enhances maximal oxygen consumption and spare respiratory capacity but triggers excessive ROS production. This ROS generation fuels SASP-mediated inflammation (IL-4, IL-6, IL-8, IL-9, interferon-γ(IFN-γ)), accelerating immunosenescence and leading to a Th17 profile [119, 126]. Furthermore, in aging CD8 + T cells, ROS-induced mtDNA leakage similarly activates cGAS/STING/IRF3, exacerbating inflammation and immune decline. The effects are mitigated by NMN supplementation [127]. These studies

show an interesting result that aging may act differently on various stages of T cells, though all of them lead to immunosenescence.

Normally, age-related failures in mitochondrial quality control worsen the mitochondrial quality. In aged CD4 + T cells, autophagic deficits permit the accumulation of damaged mitochondria, declining mitochondrial function accompanied by reduced mitochondrial protein expression [128]. A similar phenomenon is observed in macrophages. Guanylate binding protein 1 (Gbp1), under normal conditions, eliminates inflammation-induced dysfunctional mitochondria via autophagy. However, downregulated GBP1 in macrophages from aged, high-fat diet-fed mice disrupts mitophagy, induces cellular senescence and promotes the secretion of SASP factors through AMPK-p53 pathway [129].

Pathological factors synergistically amplify mitochondrial damage and then promote aging in immune cells. For example, amyloid beta (Aβ) exacerbates ROS production and loss of mitochondrial membrane potential in microglia through the inhibition of the sirtuin 1 (SIRT1)/NRF2 pathway, a key regulator of mitochondrial health. This leads to a reduced phagocytic function. Promisingly, aspirin can alleviate this [130]. Furthermore, quinolinic acid (QA), a neurotoxic metabolite produced during the aberrant activation of microglia, inhibits mitolysosome formation, impairing the clearance of damaged mitochondria. Mitophagy inducers have been shown to inhibit this process [131]. Finally, human immunodeficiency virus-1 transcription activator (HIV TAT) elevates miR505 to inhibit the deacetylase SIRT3, exacerbating antioxidant deficiencies [132].

As mentioned above, excessive ROS production in aging immune cells is caused by dysfunctional mitochondria. In senescent immune cells, a decline in the mitochondrial membrane potential, the ATP synthesis, the autophagy and the accumulation of leakage mtDNA (induced by reducing the mammalian target of rapamycin (mTOR)/TFEB signaling pathway, the mitochondrial 8-oxoguanine DNA glycosylase (mtOGG1) expression and the PTEN-induced kinase 1(PINK1)/Parkin-mediated polyubiquitination of mitochondria) results in the dysfunctional mitochondria accumulation, amplifying ROS generation. Notably, while mtOGG1 declines similarly in aged male and female mice, only males respond to mtOGG1 overexpression therapies, highlighting unresolved sex-specific regulatory mechanisms [127, 133, 134]. ROS can promote inflammation by activating c-Jun N-terminal kinase (JNK) kinase through mitochondria-to-nucleus retrograde signaling, inhibiting the suppression of 53BP1 on double-strand break (DSB) end resection. This triggers cytoplasmic chromatin fragments (CCFs) release, activating the cyclic GMP-AMP synthase (cGAS)/ stimulator of interferon genes (STING)/ nuclear factor kappa-B (NF-κB) pathway to drive SASP [135].

Mitochondria-derived inflammation is also prominent in the central nervous system (CNS). The mtDNA-triggered cGAS/STING signaling upregulates type I interferons in microglia, oligodendrocytes, and astrocytes and promotes chronic inflammation in the brain, while microglial tumor necrosis factor-α (TNF-α) induces adhesion molecules vascular cell adhesion molecule-1 (VCAM1)/intercellular Cell Adhesion Molecule-1 (ICAM1) expression in brain venous endothelial cells in the aged subventricular zone (SVZ), finally promoting T cell infiltration [136, 137]. Furthermore, aged microglia secret CCL3 to recruit peripheral CD8 memory T cells. These infiltrating T cells then release Ccl4, Ccl5, IFN-γ, X-C motif chemokine ligand 1 (Xcl1), Factor-related apoptosis ligand (Fasl) in the aged SVZ, contributing to the formation of chronic inflammation [136]. Unfortunately, although studies have found that chronic inflammation in the elderly leads to psychomotor slowing [138], the relationship between the functional changes and the molecular mechanisms described above, or the impact of these on the physiological function of the elderly, is not yet fully understood. Furthermore, ROS overproduction impairs antigen processing in aging dendritic cells, where non-functional mitochondria, rather than mitochondrial mass contribute to reducing cross-presentation efficiency of cell-associated antigens and CD8 + T cell priming, exacerbating the immune dysfunction observed in aging [128, 139]. Mitochondrial permeability transition (PT) is another key feature of aging immune cells. It can lead to the mitochondrial dysfunction. In aging lymphocytes, mitochondrial PT is more easily activated, collapsing mitochondrial membrane potential, depleting ATP synthesis, and disrupting calcium homeostasis. These changes weaken lymphocyte signaling, contributing to immune dysfunction in aging [140, 141].

Mitochondrial metabolic reprogramming also plays a key role in immunosenescence. In aging T cells, SIRT1, a negative regulator of T cell activation, suppresses glycolysis via deacetylation of phosphoglycerate mutase-1 (PGAM-1), influencing immune function [142]. In addition, senescent macrophages shift toward pro-inflammatory M1 phenotypes with elevated glycolysis and inhibited mitochondrial respiration, mediated by mTOR-hypoxia inducible factor-1α (HIF1α)-glycolysis [143], mitogen-activated protein kinase (MAPK)-NFκB [144], and Toll-like receptor 4 (TLR4)-STAT1 [145] pathways. Notably, ROS- ataxia telangiectasia mutated (ATM)-checkpoint kinase2 (Chk2) activation enhances glycolysis through pyruvate kinase M2 (PKM2) phosphorylation, facilitating M1 polarization [146]. Interventions like citrulline supplementation show promise by inhibiting

mTOR-HIF1α-glycolysis to delay immunosenescence [143].

In short, mitochondrial dysfunction is a central driver of immunosenescence, contributing to the decline in immune function that accompanies aging. The interplay between defective mitochondrial quality control, decreased mitochondrial mass, and excessive ROS production leads to inflammatory processes that further exacerbate the aging of immune cells. Although more research is needed to fully understand the precise mechanisms behind these processes, targeting mitochondrial dysfunction offers promising therapeutic avenues to alleviate the effects of aging on the immune system and improve immune responses in older individuals.

Cellular senescence

Cellular senescence, which has already been illustrated in other parts, exhibits its biomarkers, such as senescence-associated β-galactosidase (SA-β-Gal), cyclin-dependent kinase inhibitor 1 A (CDKN1A), p16INK4a (inhibitor of CDK4), whose elevation can be observed in nearly all cell senescence instances [147]. While these cellular aging markers are considered universal, it is important to note that the same type of immune cells upon aging can show different aging phenotype in different physiological and pathological conditions. The unique aging phenotype of these aging immune cells in different conditions is shown in Table 1. In Table 1, the column headers denote distinct immune-cell lineages that are known to undergo senescence, while each row lists functional or phenotypic descriptors (e.g., SASP cytokines, cytotoxicity loss,

Table 1 The summarization of the functional changes of senescent immune cells under different conditions

	Neutrophils	Macrophages	T cells	B cells	NK cells
Inhibiting apoptosis	Sepsis [393]				
Dysregulation of phagosomal function	Cystic fibrosis (CF) [394]				
Secretion of exosome (piR-17560)	Breast cancer [395]				
Impairing phagocytic activity	Atopy [396]				
Higher phagocytic activity	Endotoxemia [397, 398]				
NETs formation	Endotoxemia [397, 398]				
Inflammation	Psoriasis [399]	Neuroinflammatory phenotype [400], Alzheimer's disease (AD) [401], atherosclerosis [402], osteoporosis (SOP) [403, 404], obesity [405]	Rheumatoid arthritis (RA) [406], Severe infection [407], Brown adipose tissue [408], Elderly hypertension [409], Inflammatory bowel disease [410]		
Secretion of grancalcin		Fracture [411]			
Expression of fibrosis-associated factors		Pulmonary fibrosis (IPF) [412–414]			
Production of Arginase-1		Glioblastoma [415]			
Anti-tumor immunity			Melanoma [251, 416, 417]		
TCR signaling			Lupus [418, 419]		
Secretion of granzyme B (GZMB) and perforin-1 (PRF1)			Bacterial infection [420] (Increased)		Depression [421] (Decreased)
Delayed anti-virus ability			Systemic viral infection [83, 422]		
Reduced IL-7R expression			Primary Sjögren's syndrome (pSS) [423]		
Decreased vaccine response				Obesity [424], HIV [425]	
Decreased IgA production				Ileum infection [426]	
Cytolytic activity					Chronic circadian disruption [427]

metabolic shift) that have been reported for the corresponding senescent subset.

Besides, it is necessary to indicate that the aging of these immune cells, which lead to immunosenescence, is promoted by the "niche" comprised by stromal cells. For example, in liver cancer, laminin subunit alpha 4 (LAMA4) expressed by CD90 + eCAFs binds to integrin subunit alpha 6 (ITGA6) on the surface of T cells, activating downstream RAS signaling pathways and DNA damage responses, leading to CD8 + T cell senescence [148]. Apart from contacting directly, CAFs also secrete TGF-β to transform neutrophils into a tumor-promoting phenotype, accelerating the exhaustion of CD8 + T cells and forming an immunosuppressive microenvironment [149].

Fortunately, there exists agent which could reduce cellular senescence. Senolytic agent, plus STING inhibitor, could reduce the burden of stressed aging macrophages, improve mitochondrial integrity, and suppress STING, which will lead to overactivated inflammation after virus infection in aging mice and result in poor result. Finally, aging mice will be protected from respiratory infection after senolytic agent plus STING inhibitor treatment [150].

Hematopoietic stem cells (HSCs) myeloid bias

Aging reshapes hematopoietic stem cell (HSC) differentiation, favoring myeloid over lymphoid lineages (Fig. 2c). This phenomenon is independent of the proliferative and self-renewal abilities of HSCs but is mediated by changes in the clonal composition of the HSC compartment, ultimately leading to immunosenescence [151, 152]. Single-cell RNA-seq in aged mice shows preserved HSC proliferation; however, HSCs in aged mice exhibit delayed differentiation which occurs before the point that splits lymphoid fate from myeloid fate due to reduced Wnt signaling, probably linked to myeloid bias [153, 154]. Interestingly, when further searching the mechanism of myeloid bias, it has been observed that the impact of aging on HSCs varies among different subpopulations: the proportion of aged cells is significantly lower in myeloid-biased subsets compared to those lymphoid-biased [153]. Despite regarding the aging HSCs as a whole, this underscores the necessity of utilizing single cell sequencing techniques to subgroup aged individual's HSCs based on their distinct functions and characteristics for further investigation. Biological noise, an indicator of variability in gene expression, is considered a potential driving force behind cellular differentiation. Notably, elevated biological noise in delta-like 1 homologue (Dlk1) expression (quantified by VarID2, a model based on single cell RNA-seq) correlates with myeloid bias. Dlk1 + LT-HSCs demonstrate enhanced in vivo and vitro self-renewal, contradicting previous views of age-independent whole HSC self-renewal [151, 152, 155]. This enhanced self-renewal and expansion capacity of myeloid-biased subsets have also been corroborated by another study with single-cell sequencing, driving clonal dominance in aged HSCs [156]. These findings highlight that bulk HSC analyses mask critical subset-specific functional differences underlying myeloid bias, necessitating single-cell approaches to dissect subset-driven mechanisms.

Many studies explored the mechanisms behind myeloid bias. The decreased CUL4-ROC1 E3 ubiquitin ligase (CRL4)/ DDB1 And CUL4 Associated Factor 1 (DCAF1)-mediated ubiquitination degradation signaling in aged HSCs leads to reduced ubiquitination of pseudouridine synthase 10 (PUS10), resulting in increased PUS10 level and myeloid differentiation [157]. Elevated period circadian clock 2 (Per2) in lymphoid-biased HSCs triggers p53 phosphorylation, selectively inducing apoptosis and depleting lymphoid subsets [158]. Aging increases platelet-biased HSCs, which enhance myeloid output while suppressing lymphoid-biased HSCs through competitive clonal dominance [159].

The occurrence of myeloid bias may be related to changes in the aging bone marrow niche. Elevated IL-1β and TNF-α levels, produced by dysfunctional stromal cells, promote myeloid differentiation and inhibit B-cell generation via chronic, low-grade inflammation [160–162]. Importantly, transplantation studies demonstrate that aged lymphoid-biased HSCs regain normal differentiation in young microenvironments, indicating the microenvironment-dependent reversibility of myeloid bias [162]. Some studies have found that this reversible bias is associated with epigenetic modifications [163]. Polycomb-group proteins promote and maintain cellular differentiation by suppressing gene expression, and genes associated with myeloid differentiation, which are non-Polycomb targets, show hypomethylation as well as high expression with increasing age, contributing to increased myeloid differentiation [164]. The downregulation of histone acetyltransferase Kat6b impairs multilineage differentiation in aging long-term (LT)-HSCs, leading to myeloid bias [165]. Notably, non-HSC sources compensate for most lineages except lymphocytes (particularly T cells), ultimately driving myeloid bias characterized by lymphoid reduction [166].

Multiple strategies aim to reverse this bias. Glycyrrhizic acid (GA) enhances lymphoid (especially CD8 + T cell) differentiation in Lin-CD117 + HSCs of aged mice by binding S100 calcium-binding 8 (S100A) protein, reshaping immunity [167]. Similarly, fecal microbiota transplantation (FMT) promotes HSC lymphoid differentiation via inflammation reduction and forkhead box protein O1 (FOXO1) upregulation, while reshaping gut microbiota metabolism to restore hematopoiesis through

Lachnospiraceae expansion and tryptophan-associated metabolites [168]. Clinical efficacy remains unconfirmed.

Altered intercellular communication

Intercellular communication within the immune system primarily involves neuro-humoral regulation and intercellular signaling molecule exchange, with the latter predominantly manifesting as SASP, elucidated extensively elsewhere in the article. Here, the focus lies on the impact of neuro-humoral regulation on immune system aging (Fig. 3). Thymic involution, a key aging hallmark, is linked to age-related anterior hypothalamic changes, though its regulatory role remains debated. Intriguingly, anterior hypothalamic lesions suppress splenic and peripheral blood lymphocytes, reversible via thyrotropin-releasing hormone (TRH) acting directly on lymphocytes rather than the thyroid [169–171]. Apart from lymphocytes, corticotropin-releasing hormone (CRH) reduces splenic NK cell activity and cytotoxicity in aged rats, which reduces the immune function [172]. Additionally, declined pineal melatonin exacerbates thymic involution and reduces lymphocytes in peripheral blood and spleen. Melatonin treatment or pineal grafts restore immune function in aged mice [173].

Hormonal dysregulation also impacts aging immune cells in age-related diseases. For instance, melatonin can inhibit choroidal neovascularization (CNV) by suppressing M2 polarization of aging macrophages/microglia through the IL-10/STAT3 pathway, offering potential targets for treating CNV and other age-related eye diseases [174].

Finally, hormones are involved in regulating the individual's circadian rhythm, which is no exception for the aging immune system. In elderly subjects, total B cells inversely correlate with daytime cortisol, whereas helper/inducer T cells show positive correlations. Conversely, morning cortisol negatively associates with total T lymphocytes but positively links to suppressor/cytotoxic T cells [175]. These circadian-linked immune-cortisol relationships differ from younger individuals, though their functional relevance requires further study.

Chronic inflammation

Mild chronic inflammation, a hallmark of aging, drives age-related damage and diseases (Fig. 1c). Aging elevates inflammatory biomarkers (IL-6, IL-8, IL-2, IFN-γ, TNF-α) [176–178], reflecting heightened inflammation. Among these biomarkers, while IL-6 was traditionally viewed as a key marker, recent evidence suggests TNF-α better indicates chronic inflammation—though this is confined to community-dwelling elders with mild inflammation and requires broader validation [179].

There has been some research which found that central immune system exists chronic inflammation when aging. And the details have been mentioned above. Besides, a study suggests that elevated blood mtDNA correlates

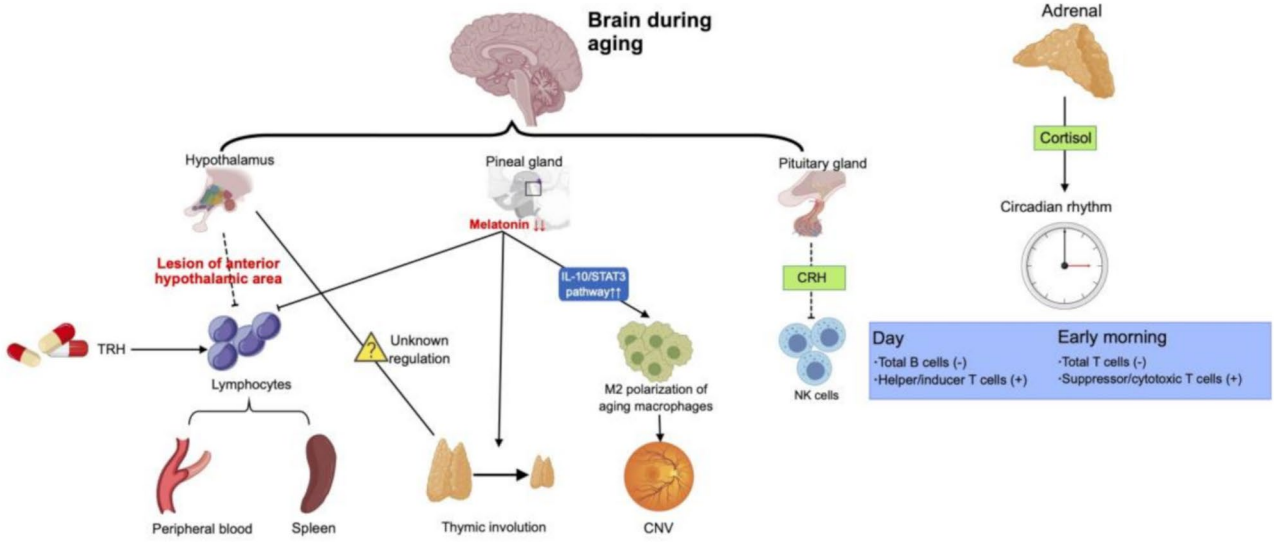

Fig. 3 Neuroendocrine regulation in immunosenescence. Involution of thymus is found to be associated with age-related changes in the regulation of the anterior hypothalamic area, although the role of the hypothalamus in either positive or negative regulation of the thymus remains contentious. Lesion of anterior hypothalamic area exerts inhibitory effects on lymphocytes in the spleen and peripheral blood. This aberration can be ameliorated by administering thyrotropin-releasing hormone (TRH), which acts directly on the lymphocytes. Moreover, CRH leads to decreased splenic NK activity and cytotoxicity. Additionally, decreased melatonin with aging also leads to the involution of thymus, decreased numbers of lymphocytes in peripheral blood and spleen, and M2 polarization of aging macrophages/microglia, which causes CNV. Besides, hormones are involved in regulating the aging individual's circadian rhythm. For example, total B cells correlate negatively with cortisol during the day, while helper/inducer T cells correlate positively with cortisol; in the early morning, total T lymphocytes correlate negatively with cortisol, while suppressor/cytotoxic T cells correlate positively with cortisol

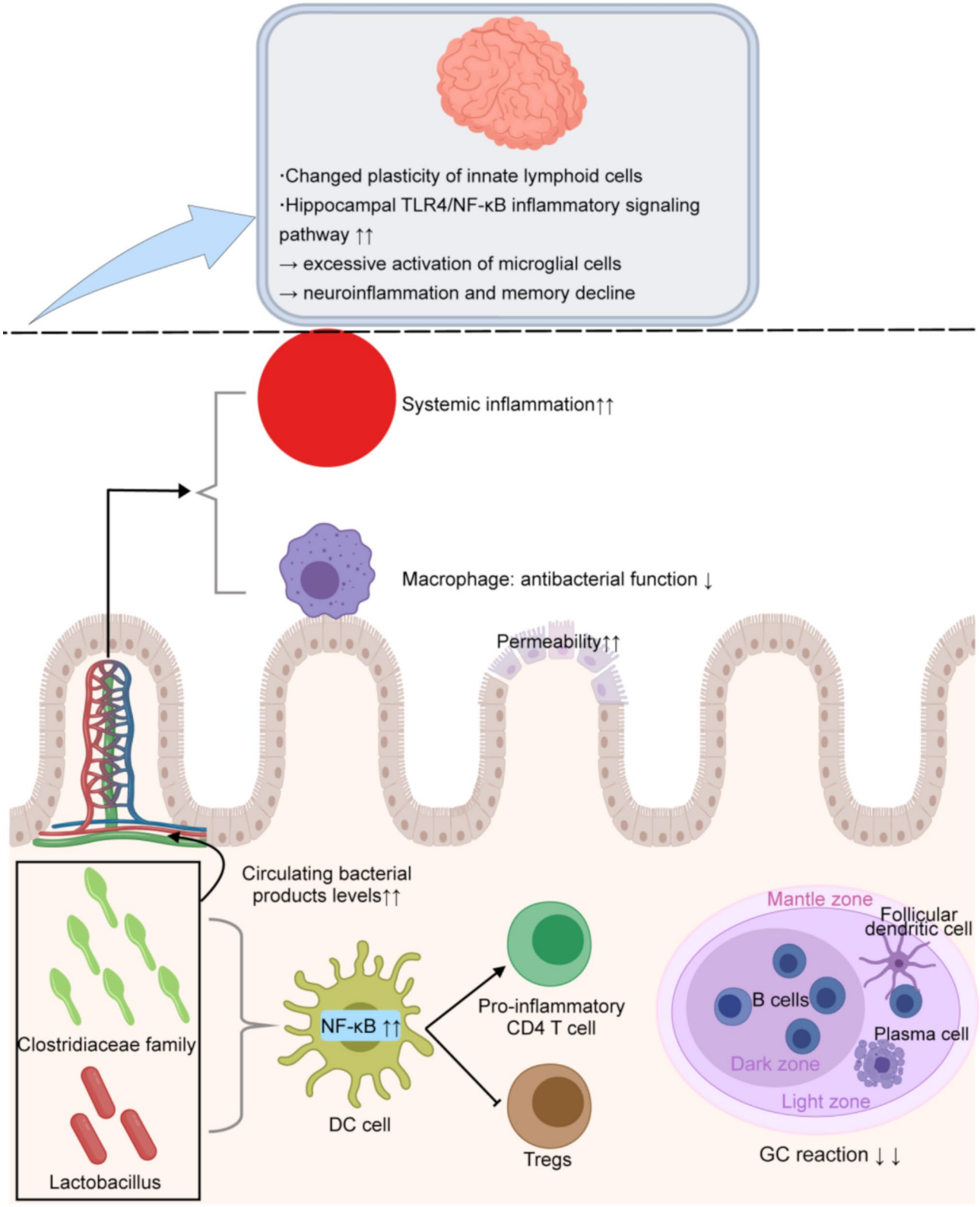

Fig. 4 (See legend on next page.)

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Fig. 4 Gut dysbiosis with aging induces immunosenescence and influences brain-gut axis. Aging individuals often experience gut dysbiosis, characterized by an increase in harmful bacterial genera a decrease in beneficial genera. This dysbiosis can lead to the activation of NF-κB signaling pathway of dendritic cells (DCs). Ultimately, this activates pro-inflammatory CD4 T cells while inhibiting Tregs induction. Additionally, the germinal center (GC) reactions in the gut decrease, manifested by a reduction in the frequency and quantity of B cells in the GC. Moreover, age-related gut dysbiosis triggers increased intestinal epithelial permeability and circulating bacterial products levels, exacerbating systemic inflammation and impairing macrophages' antibacterial function. These systemic inflammatory changes can also affect the central nervous system, including altering the plasticity of innate lymphoid cells in the brain and the increased hippocampal TLR4/NF-κB inflammatory signaling pathway

with elevated inflammatory biomarkers (TNF-α, IL-6, regulated upon activation normal T cell expressed and secreted (RANTES), and IL-1ra), implying that the inflammatory mechanisms present centrally may also exist peripherally [180]. Consistent with this study, in age-related hearing loss (ARHL), cochlear and cochlear nucleus (CN) inflammation driven by macrophages, microglia and complement component 1q (C1q deposition) involves NF-κB pathway and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome rather than cGAS-STING [181]. In addition to the nervous system, aging visceral adipose tissue (VAT) also exhibits increased tissue-resident memory γδ T cells (CD44hi62LlowCD69+) with a significant increase in the percentage and total quantity of pro-inflammatory IL-17 A + γδ T cells, which upregulates IL-17 A to promote chronic inflammation by inducing IL-6 production in preadipocytes/adipose-derived stem cells(ADSCs) [182].

Surprisingly, there have been clinical researches indicating that anti-inflammation is a prospective direction in reversing immunosenescence. Coffee consumption decreases the frequency of senescent T cells and the levels of the SASP by downregulation of the Janus kinase (JAK)/STAT and MAPK signaling, suggesting that coffee has anti-immunosenescence effects [183]. Besides, treating diabetic subjects with senolytic drug dasatinib plus quercetin (D + Q) shows reduced blood SASP factors after 11 days, though the mechanism remains unclear [184]. Dietary interventions in aging animals mitigate chronic inflammation: zinc supplementation lowers IL-6, monocyte chemotactic protein 1 (MCP1), and inflammatory cytokines of Th1/Th17 while boosting naïve CD4 + T cells [185]. Furthermore, *L. paracasei* KW3110 alters gut bacterial composition, reduces CD4 + T cells, which produce IFN-γ in the lamina propria of the small intestine (SI-LP), and the serum proinflammatory cytokines, to alleviate intestinal and retinal inflammation [186]. High-fiber diets elevate the butyrate-producing bacteria in the gut, dampening microglial proinflammatory signals to reduce central chronic inflammation [187]. Ingestion of silk peptide in aging mice reduces splenic mass and M1 macrophages in the gastrocnemius muscle, thereby ameliorating low-grade chronic inflammation in skeletal muscle [188]. However, human applicability remains uncertain. Adherence to EAT-Lancet or Mediterranean diets shows only minor, non-significant reductions in inflammatory biomarkers, potentially due to balanced nutrient profiles lacking targeted components [189]. Further research is needed to validate dietary strategies in humans.

Gut dysbiosis

Aging-associated gut dysbiosis, marked by increased harmful bacterial genera of the Clostridiaceae family and decreased beneficial genera like Lactobacillus within the Firmicutes phylum (Fig. 4), functions as a potent microenvironmental regulator. This dysbiosis creates conditions that indirectly trigger DCs' NF-κB activation via microbial factors, impairing tolerance and migration of DCs. Ultimately, this promotes pro-inflammatory CD4 + T cells while suppressing regulatory T cells (Tregs) induction. Specific dysbiosis-derived factors and functional consequences require further study [190]. Moreover, age-related dysbiosis elevates gut permeability and circulating microbial products, worsening systemic inflammation and compromising macrophages' antibacterial function. Such inflammation impacts the central nervous system: in aging mice, dysbiosis disrupts brain and gut innate lymphoid cell plasticity, linking gut changes to age-related brain alterations [191].

Targeting gut dysbiosis alleviates immunosenescence in animal models. Fecal microbiota transplantation (FMT) between young and aged mice in the same strain restores the frequency and quantity of B cells in germinal center (GC) via adjuvant-like manner, highlighting strain-specific efficacy [192]. Probiotics prevent dysbiosis by enhancing bile salt hydrolase activity and gut taurine levels to reinforce tight junctions [193–195]. Additionally, certain substances can indirectly alleviate inflammation by modulating gut microbiota composition. For example, tea polyphenols improve intestinal flora composition and diversity to inhibit the hippocampal TLR4/NF-κB signaling induced by gut dysbiosis and increased gut permeability, which can trigger microglia-driven neuroinflammation and memory decline [196]. Lastly, a high-tryptophan diet reduces pro-inflammatory *Acetatifactor*, *Enterorhabdus*, and *Adlercreutzia* genera [197].

Improving gut dysbiosis may enhance immunotherapy efficacy, potentially countering immunosenescence. Aging patients with enterotype/aging-enriched (E/AE), namely enriched *Bacteroides*, *Clostridiales*, *Bilophila* and *Faecalicatena* exhibit heightened immunotherapy sensitivity, transplanting this enterotype into aged mice boosts

anti-PD-1 response [198]. The other research found that the decreased response of fused in sarcoma (FUS) and calreticulin nanoparticles (CRT-NP) in aging mice is due to the diminished alpha diversity, which is an indicator of intestinal microbial ecosystem [199]. These findings suggest gut dysbiosis as a potential prognostic marker for immunotherapy, though its utility may vary by cancer type and therapeutic approach.

A number of recent articles have described how these features of immunosenescence play a role in older tumor patients. These features are summarized in Table 2. Based on this table, it is obvious that for some hallmarks, the relationship between them and tumor is still mysterious, and if they have treatment potential targeting tumor remains unknown.

The eleven hallmarks of immunosenescence are highly interconnected rather than isolated, collectively driving immune dysfunction. Genomic instability and telomere attrition contribute to cellular senescence, which interacts with epigenetic alterations that regulate immune phenotypes and are in turn influenced by chronic inflammation, forming a vicious cycle. Loss of proteostasis, often linked to disabled autophagy, impairs immune functions like antigen presentation. Mitochondrial dysfunction amplifies inflammation through pathways such as cGAS/STING, interacting with autophagy and proteostasis mechanisms. These processes drive cellular senescence and its associated secretory phenotypes, which along with hematopoietic stem cell myeloid bias, altered intercellular communication, and gut dysbiosis, further disrupt immune signaling and cell composition. Chronic inflammation, a central feature arising from multiple hallmarks, exacerbates other dysfunctions, leading to impaired immune surveillance, reduced cytotoxic responses, and systemic immunosuppression.

Effects of aging on systemic immunity in tumor patients

Cancer incidence rises with age, likely due to heightened tumor susceptibility. An overview of how aging influences systemic immunity in tumor patients has been shown in Fig. 5. Aging promotes bladder carcinogenesis induced by the BCa carcinogen N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) with increased neutrophil and monocyte infiltration, though the molecular mechanism remains unclear [200]. Aging also contributes to

Table 2 Hallmarks of immunosenescence: associations with tumor risk, patient prognosis, and response to immunotherapy

Hallmarks	Correlation with tumor patients	Correlation with immunotherapy response	Mechanism
Genomic instability	/	/	/
Telomere attrition	Increased risk of tumor for T cell defects [428]	/	/
Epigenetic alterations	Accelerated tumor metastasis [429]	Resistance to anti-PD-1 immunotherapy	Upregulation of E3 ubiquitin ligase BFAR in aged CD8 + T cells, activating a deubiquitinase USP39, finally inhibiting JAK2-STAT pathway, leading to a decline of tissue resident memory T (TRM) cells
	Poor survival [430]	Limited durability of anti–PD-L1 therapy	Inducing CD8 + T cell exhaustion by Asxl1, which controls the deubiquitination of histone 2 A lysine 119
Loss of proteostasis	/	/	/
Disabled autophagy	/[431]	Short progression-free survival and overall survival after PD-1 blockade therapies	Transferring mitochondria with mtDNA mutations from cancer cells into CD8+ T cells, which don't undergo mitophagy, thus causing CD8 + T cells dysfunction
Mitochondrial defects	Accelerated tumor metastasis [277]	/	The opening of mitochondrial permeability transition pore channels to release mtDNA and lead to the mitochondria-dependent vital NETs formation in tumor-associated aged neutrophils (Naged, CXCR4 + CD62Llow)
Cellular senescence	Poor overall survival and event-free survival [432]	/	T-cell senescence and exhaustion
	Poor progonosis [433]	/	Impairing T-cell function and facilitates tumor immune evasion
	Higher mortality [434]	Less responsive to immunotherapeutic agents	T cell senescence and down-regulation of immune checkpoint genes
Hematopoietic stem cells (HSCs) myeloid bias	/	/	/
Altered intercellular communication	Poor patient survival [300]	/	T cell senescence induced by ILT4 derived from tumor cells
Chronic inflammation	Higher recurrence and poor prognosis [435]	/	Accumulation of myeloid progenitor-like cells which promotes IL-1α
Gut dysbiosis	/	/	/

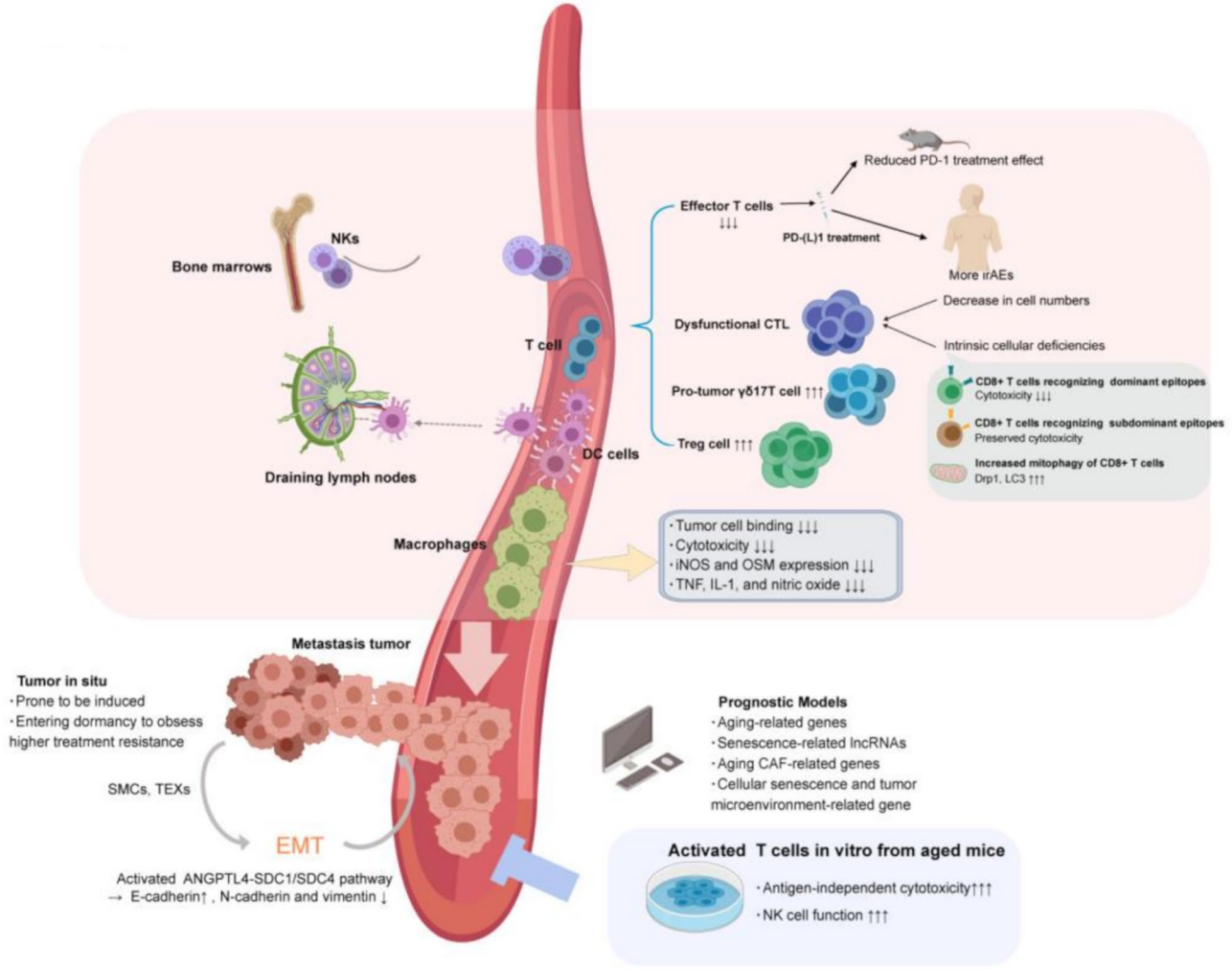

Fig. 5 Systemic immunity in aging patients with tumor results in worse prognosis. The incidence of cancer increases with age, likely due to enhanced susceptibility to tumor. Tumor in aging population also easily enters dormancy to evade treatment, it acquires resistance of, for example, PD-(L)1 treatment, by reducing effector T cells in aged mice. However, this treatment doesn't show prognostic difference in humans. Apart from effector T cells, other T cells, including, dysfunctional T cells, pro-tumor γδ17 T cells and Treg cells also present exceptions in aging tumor patient, and obviously, they bring about immunosenescence, leading to decreased immunity. Based on this, to better predict the treatment outcomes and prognosis of aging-related cancers, prognostic models based on ARGs, senescence-related lncRNAs, aging CAF-related genes and cellular senescence and tumor microenvironment-related genes have been established in various cancers. When talking about the relationship between aging and tumor metastasis and progression, there exist different opinions. Most of the time, T cells mentioned above, as well as SMCs, DCs and NKs, work together to form immunosenescence, which leads to the pro-tumor immune environment. However, T cells activated in vivo show NK cell function, through which these T cells have increased antigen-independent cytotoxicity. This may relate to an anti-tumor immune environment in some tumor-based mice

heightened treatment resistance of tumor. Senescent bone marrow mesenchymal stem cells induce the dormancy and the inhibited proliferation of bone-metastasized breast cancer cells (BCCs) via SASP-mediated p21 upregulation, enabling treatment evasion [201]. Tumor could also acquire resistance by reducing effector T cells, which is the target cells for some treatments. Aged mice resist PD-1 blockade therapy due to elevated CD45RB in naïve CD8 + T cells, which suppresses TCR signaling and reduces generation of the CD44lowCD62Llow (P4) subset. This subset, derived from naïve T cells and marked by high one-carbon metabolism gene expression, differentiates into effector T cells in vivo to reject tumors. Strong immune stimulation by non-self-cells reverses TCR inhibition, restoring CD8 + T cell antitumor immunity [202]. However, clinical trials show similar anti-PD-1/anti-PD-(L)1 efficacy across ages, but elderly face higher immune-related adverse events (irAEs), which may be related to a higher rate of treatment discontinuation [203, 204]. The phenomenon is reasonable, because PD-1 is expressed on many types of immune cells, such as macrophages, B cells, T cells, dendritic cells [205]. This means that when taking the treatment effect of PD-1 blockade on human into consideration, the

possible influence of PD-1 blockades on other immune cells, beside T cells, should also be considered. Interestingly, although aging is generally considered a risk factor for higher cancer mortality, recent studies suggest that this may vary across different types of cancer. Immune checkpoint reduction in the microenvironment worsens outcomes in 16 cancers (e.g. breast cancer, acute myeloid leukemia) due to suppressed adaptive immunity, while in glioblastoma/rectal adenocarcinoma, this aging-related molecular characteristics and outcomes differences have not been observed [206].

Based on this, to better predict the treatment outcomes and prognosis of aging-related cancers, prognostic models based on aging-related genes (ARGs) have been established in various cancers, including lung cancer [207–209], melanoma [210–213], glioblastoma [214], renal cell carcinoma [215], acute myeloid leukemia (AML) [216], high-grade serous ovarian cancer [217], colorectal cancer [218, 219], breast cancer [220, 221], head and neck squamous cell carcinoma (HNSCC) [222, 223], hepatocellular carcinoma (HCC) [224], diffuse large B-cell lymphoma (DLBCL) [225], pancreatic adenocarcinoma [226], and glioma [227]. These models consistently link high-risk tumors to worse immune checkpoint inhibitor (ICI) effect despite heterogeneous ARGs. Similarly, the method of establishing prognostic models based on cell senescence-related lncRNAs has been applied in glioma [228], HNSCC [229], HCC [230], and colorectal cancer [231, 232]. Additionally, an innovative study developed a prognostic model based on aging CAF-related genes (ACAFRGs) to predict the prognosis and response to immune checkpoint blockade therapy in low-grade gliomas (LGGs) [233]. Finally, the combination of CellAge and TME scores, based on cellular senescence and tumor microenvironment-related gene expression, can serve as an independent prognostic factor and predictor for immunotherapy outcomes in hepatocellular carcinoma (HCC) [234]. In summary, the effectiveness of these different models for the same tumor type requires further comparison.

It is worth noting that the relationship between aging and tumor metastasis and progression remains inconclusive. Some studies suggest that aging may promote tumor progression by impairing the immune system. This is mainly associated with dysfunction of cytotoxic T lymphocyte (CTL) cells [235], proliferation of pro-tumor γδ17-T cells [236], and an increase in immunosuppressive Treg cells [237]. Early studies debated whether age-related CTL cytotoxicity decline stemmed from reduced cell numbers or intrinsic defects [238, 239]. However, a recent study suggests that both factors may contribute to CTL cell dysfunction. Aged mice show decreased total CD8 + T cells but increased proportions recognizing dominant/subdominant epitopes. Notably, dominant epitope-specific CD8 + T cells exhibit reduced cytotoxicity versus young mice, while subdominant-targeted cells maintain function, potentially explaining accelerated tumor progression in aging. Chemotherapy differentially affects epitope-specific T cells, suggesting therapeutic potential in expanding subdominant-targeted CD8 + T cells [240]. Additionally, senescent-like myeloid cells (SMCs) and exhausted T cells (TEXs) promote epithelial-mesenchymal transition (EMT)-mediated liver metastasis in metastatic colorectal cancer (mCRC) via angiopoietin like 4 (ANGPTL4)-syndecan 1 (SDC1)/SDC4 pathway, upregulating E-cadherin and downregulating N-cadherin and vimentin of cancer cells [241]. Moreover, aging triggers mitochondrial sphingosine kinase 2 (SphK2)/sphingosine-1-phosphate (S1P) signaling in T cells, suppressing HDAC1/2 and promoting CerS6-mediated C14 ceramide accumulation. This suppresses protein kinase A (PKA) activity, reducing dynamin-related protein 1 (Drp1)'s inhibitory S637 phosphorylation to enhance Drp1-driven mitophagy, impairing mitochondrial function and anti-tumor efficacy in activated CD8 + T cells. Elevated microtubule-associated protein 1 light chain 3 (LC3) synergizes mitophagy activation by recruiting autophagosomes, though its precise mechanism needs clarification [242]. In innate immunity, aging amplifies IL-17 in the T-cell zone of peripheral lymph nodes (pLNs), skewing γδT cells toward γδ17 subsets that activate in tumor-draining lymph nodes, infiltrate tumors, and accelerate growth—despite preserved transcriptomic and functional profiles in aged γδT cells [236]. Finally, aged lung cancer models exhibit age- and tumor-dependent splenic CD4 + CD25 + Foxp3 + Treg expansion, though underlying causes remain unclear [237].

In addition to T cells, other immune cells also contribute to the acceleration of tumor progression associated with aging. Aged DCs show impaired CD8 + T cell priming in vitro and reduced migration to lymph nodes and weaker stimulation of T cell immune responses in vivo, linked to defective CCR7-mediated chemotactic responses [243]. Moreover, combining autologous DC vaccines with anti-CD134 or anti-CD137 monoclonal antibodies rescues anti-tumor responses, implicating co-stimulatory deficits in age-related DC dysfunction [244]. Furthermore, aged macrophages exhibit suppressed tumor cell binding, cytotoxicity, and reduced expression of inducible nitric oxide synthase (iNOS), Oncostatin-M (OSM), TNF, IL-1, and nitric oxide, correlating with diminished anti-tumor activity [245, 246]. NK cells in aged mice also display functional impairments, associated with reduced output from bone marrow and compromised tumor-targeting ability [247].

While aging is frequently associated with immune dysfunction that accelerates tumors, some studies

paradoxically suggest slowed tumor growth and metastasis in aged individuals. Proposed mechanisms include reduced tumor cell proliferation [248], increased apoptotic cell death [249] and impaired angiogenesis [250]. Additionally, recent research suggests that the deceleration of tumor progression associated with aging may also be related to the immune system. CD8 + T cells from aged mice, when activated in vitro, display heightened antigen-independent cytotoxicity and adopt NK-like function. This shift may stem from age-related menin downregulation, which increases enhancer binding and cytotoxic gene expression such as CD244, killer cell lectin like receptor B1c (Klrb1c), Fc fragment of IgE receptor Ig (Fcer1g), and NK-associated molecules, ultimately suppressing tumor metastasis in aged mice. Thus, aging may exert dual, context-dependent effects on tumor dynamics via divergent immune and cellular pathways [251].

In summary, while there are still many mysteries surrounding the relationship between aging, tumors, and systemic immunity, aging and young tumor patients exhibit distinct immune responses, offering opportunities for improved elderly cancer therapies. Age-targeted treatments (e.g., apoptosis-inducing agents, hydrocortisone, adriamycin, anti-angiogenic agent TNP-470, and immunomodulators like Levamisole and Bacille Calmette-Guérin (BCG)) demonstrate enhanced efficacy in aged versus young mice [252]. Additionally, new technological advancements, such as engineered fusokines, are believed to enable targeted anti-tumor therapy for the elderly. For instance, glioblastoma cell lines GL261 and CT2A transfected with the GIFT-7 molecule (a fusion of IL-7 and granulocyte-macrophage colony-stimulating factor (GM-CSF)), used as fusokine tumor vaccines and administered subcutaneously, significantly improved survival and reduced tumor volume in aged glioblastoma mice by regenerating thymic function and activating DC cells to recruit systemic T cells to the intracranial tumor site. Excitingly, cured mice developed CD4 + Th17-dominant immunity against glioma recurrence [253]. While these approaches require clinical safety validation, tailoring therapies to age-specific tumor immunology remains a highly promising frontier.

The eleven major molecular markers of systemic immunosenescence act synergistically to drive immune cell functional decline and systemic immune suppression. In cancer patients, this aging-related immune remodeling primarily manifests as abnormalities in T cell function and phenotype, ultimately leading to alterations in anti-tumor immune response efficacy, treatment resistance, and prognosis in elderly patients. Notably, these systemic aging characteristics not only affect the function of circulating immune cells but also profoundly reshape the ecological landscape of the tumor microenvironment (TME). The following sections will delve into how the aging process specifically alters the cellular composition, signaling networks, and functional state of the TME, elucidating its mechanisms of action on tumor progression through the microenvironment.

Immunosenescence-driven remodeling of the tumor microenvironment

As mentioned above, TME interacts with tumor cells closely. The differences between normal and aging TME are presented in Table 2. Recently, there has been the research proving the existence of age-dependent TME changes by single cell sequencing, which provides a cell atlas in TME in different ages [254]. In short, the aging TME is characterized by increased immunosuppressive cells [255], accumulation of pro-inflammatory SASP factors [256, 257], metabolic abnormalities [258] and matrix remodeling [259]. Importantly, these features of the aging TME are not isolated phenomena but represent the localized manifestation of systemic immunosenescence. For example, SASP which induces chronic inflammation, a hallmark of systemic immunosenescence, drives and sustains the pro-inflammatory and immunosuppressive TME in most cases [260, 261]. It is reported that in aging mice, the function of CD163 + tumor associated macrophages (TAMs) can be further divided into improving tumor growth (expressing peroxisome proliferator activated receptor gamma(PPARG)) and immunosuppression (expressing Ly-6 C) in intraocular melanoma [262]. Moreover, aging TAMs could also increase metastasis and proliferation of tumor. In aging mice, p16INK4a-expressing macrophages, namely aging macrophages, secrete numerous SASP factors including bone morphogenetic protein-2 (Bmp2), Ccl2, Ccl7, Ccl8, vascular endothelial growth factor A(VEGFA), etc [256, 257]. Apart from immune cells in aging TME, cancer cells and stromal cells also secrete SASP cytokines. Similarly, tumors exploit CXCL2 to induce aging of circulating neutrophils, directing their migration to the TME to fuel progression [263]. In addition, cancer-associated fibroblasts (CAFs) can secrete some special cytokines and extracellular matrix, including ROS and L-lactic acid [264], CCL2 [265], growth differentiation factor 15 (GDF15) [266], IL-8 [267], secreted frizzled-related protein 1 (SFRP1) [268], SFRP2 [269, 375], that promote proliferation, metastasis, angiogenesis, and drug resistance [270]. In colorectal cancer, GDF15 from senescent CAFs drives proliferation, migration and invasion of tumor via PI3K/MAPK pathway [271]. Additionally, IL-6 from CAFs promotes malignancy in both cervical and pancreatic cancers [272–274].

Apart from SASP, immune cells and stromal cells also directly act on aging TME. Next, we will discuss in detail how these cells contribute to the features of aging TME

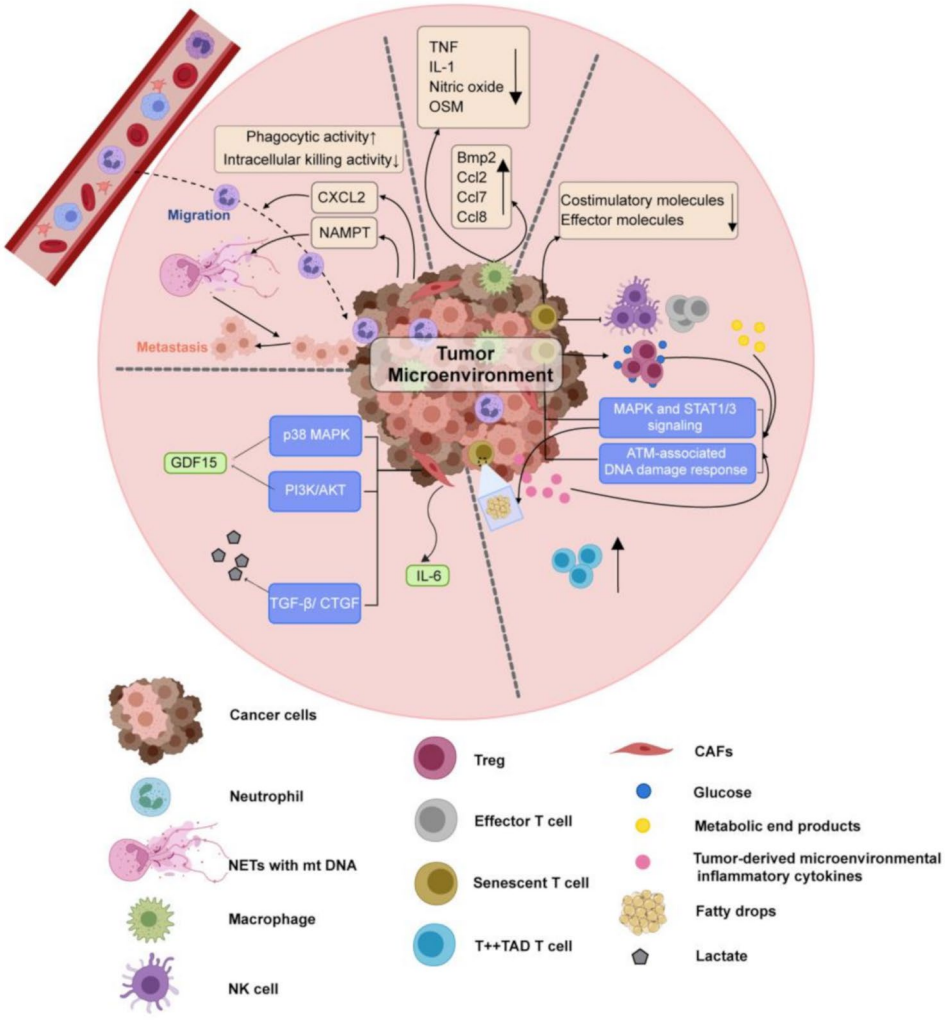

Fig. 6 Altered TME in aging tumor patients. TME interacts with tumor cells closely. Tumor-associated aged neutrophils (Naged, CXCR4hiCD62Llow) have NETs mainly consisting of mitochondrial DNA, leading to a function as promoted the lung metastasis of breast cancer. Tumor can express CXCL2 to cause aging of circulating neutrophils, leading aging neutrophils to migrate to TME and improve tumor progression. The antitumor activity of TAMs also decreases with the decline of effector molecules including TNF, IL-1, nitric oxide, oncostatin-M (OSM) and the defect of tumor cell binding and cytotoxicity. Besides, aging macrophages, secret numerous senescence associated secretory phenotype (SASP) factors including Bmp2, Ccl2, Ccl7, Ccl8, etc. Senescent T cells affect TME mainly by downregulating costimulatory molecules and the effector molecules, inducing adaptive Treg cells, inhibiting DCs and effector T cells. Possible mechanisms about how senescent T cells influence TME focus on ATM-associated DNA damage response and activate MAPK and STAT1/3 signaling initiated by glucose competition environment created by Treg cells' accelerated glucose consumption, accumulation of metabolic end products (cAMP, adenosine, and lactate), tumor-derived microenvironmental inflammatory cytokines, and lipid metabolism. Moreover, the aged tumor microenvironment (TME) promotes the differentiation of CD8 + T cells into a unique dysfunctional subset termed tumor-infiltrating age-associated dysfunctional (T + + TAD) cells. This CD8 + T cell subset exhibits minimal cytotoxicity, resulting in impaired tumor control. Cancer-associated fibroblasts (CAFs) act on aging TME mainly by SASP through p38 MAPK pathway/PI3K-AKT signaling pathway/TGF-β-CTGF pathway. GDF15 is an essential SASP factor secreted by senescent CAFs to promotes cell proliferation, migration, and invasion through PI3K and MAPK pathway. Additionally, IL-6 is secreted by CAFs in TME

and and be reshaped by it, as well as their complex relationship with tumors (Fig. 6).

Neutrophils

Tumor-associated neutrophils (TAN) in the TME secrete pro- (ROS, reactive nitrogen species (RNS)) or anti-inflammatory (Type I IFN) signals that directly and indirectly shape tumor behavior [275]. They exert anti-tumor effects via phagocytosis, degranulation, and neutrophil extracellular traps (NETs) formation. To date, TANs are broadly classified into anti-tumor N1 (pro-inflammatory) and pro-tumor N2 (anti-inflammatory) subtypes. However, with aging, the function of TANs will change in some degrees. Aged cancer patients exhibit increased polymorphonuclear leukocyte (PMNs) phagocytosis but reduced intracellular killing capacity compared to young individuals, impairing tumor control [276]. Besides, tumor-driven aged neutrophils (Naged,

CXCR4hiCD62Llow) different from neither N1 nor N2 type of neutrophil form metastasis-promoting NETs rich in mitochondrial DNA via tumor-derived nicotinamide phosphoribosyl transferase (NAMPT). Blocking this pathway reduces breast cancer lung metastasis in mice [277]. Clinically, CXCR2 inhibitors show efficacy in breast cancer [278]. Finally, anti-B-cell lymphoma-extra large (Bcl-xL) compounds combined with GM-CSF selectively eliminate aged TANs in preclinical models, sparing normal neutrophils and young anti-tumor TANs [279]. However, platelet toxicity remains a challenge [280].

Natural killer (NK)

Natural killer (NK) cells primarily mediate antitumor immunity through cytolysis and secretion of cytokine and chemokine [281, 282]. Little research of the correlation between NK cell senescence and tumor were delivered, but almost all of them focused on the leukemia [283, 284], neither in the solid tissues nor the TME. That is, how NK cell senescence plays a role in TME remains a mystery.

Macrophages

Macrophages in TME, which always mean TAMs, is similar to TANs mentioned above. They can be divided also into two subsets, M1 (anti-tumor) and M2 (pro-tumor). Aging biases macrophage differentiation toward M2 via IL-8 and B cell leukemia/lymphoma 3 (Bcl3) in the TME [255]. Similar phenomenon of elevated M2-type macrophages were discovered in older breast cancer patients [285]. Besides, aged TMEs exhibit increased exhausted macrophages, contributing to elevated macrophage counts without enhanced antitumor capacity and cytotoxic T-cell responses [286–288]. Furthermore, senescent TAMs show reduced antitumor activity due to diminished TNF, IL-1, nitric oxide, OSM production, and impaired tumor binding and cytotoxicity [246, 289]. More seriously, expansion of CD11b + F4/80 + Ly6G – Siglec-F – macrophages in aged mesothelioma TMEs compromises IL2/anti-CD40 immunotherapy efficacy. Macrophage depletion may improve treatment outcomes in elderly patients, though mechanisms require clarification [290]. Sports show potential to counteract age-related macrophage dysfunction through polarization regulation, though mechanistic insights remain limited [291].

T lymphocytes

As mentioned above, senescence of responsive T cells is often accompanied by a decline in their function. Their functional decline contributes to immunosuppressive TMEs through downregulated costimulatory and effector molecules, induction of adaptive Treg cells and premature senescence in T cells, and inhibition of DCs and effector T cells. Nevertheless, molecular mechanisms remain unclear but may involve ATM-associated DNA damage response, MAPK/STAT1/3 activation via glucose competition created by Treg cells' accelerated glucose consumption, and accumulation of metabolites (cyclic AMP (cAMP), adenosine, lactate) and tumor-derived cytokines [258]. Specifically, not only Treg cells, tumor cells promote T-cell senescence also via ATM and MAPK pathways, while blocking these pathways enhances immuno-oncology therapies in vivo [292]. In this case, lots of trials attempted to specifically inhibit the MAPK pathway in senescence T cells to reverse it, avoiding affecting MAPK pathway with normal functions in T cells [293, 294]. Apart from the direct inhibition of MAPK pathway, TLR8 activation suppresses Treg glucose metabolism via mTOR inhibition, reversing immunosuppression and T cell senescence without affecting normal T cells, offering superior targeting potential [295]. Therefore, comparing to MAPK pathway inhibitors, TLR8 may be a better therapy target. Lipid metabolism also induces senescence in responder T cells through fatty acid droplet accumulation, engaging MAPK and STAT1/3 pathways and cytosolic phospholipase A2 (cPLA2α) expression, with Treg involvement [296]. Besides, aging increases Dectin-1 activation in mice, elevating IL-1β to amplify Treg suppression [297].

Besides, recent study has also showed the influence of aging TME on T cells. The aged TME drives CD8 + T cells toward a dysfunctional subset tumor-infiltrating age-associated dysfunctional (T + + TAD) cells characterized by PD-1, thymocyte selection associated high mobility group box (Tox), and IL-7R expression, with minimal cytotoxicity, exacerbating tumor progression in aging mice. This dysfunction stems from reduced NK cells in aged TME, which impair conventional type 1 dendritic cells (cDC1) recruitment via XCL1 and antigen presentation, blunting CD8 + T cell activation and cytotoxicity. Fortunately, CD40 agonists restore cDC1 function and CD8 + cytotoxicity by boosting myeloid cell quantity and function, offering therapeutic potential [298].

Based on these results, methods on suppressing the function of Treg cells were explored. Surprisingly, vascular endothelial growth factor receptor 2 (VEGFR2) inhibition in tumors upregulates exosome miR-3200-3p, targeting Treg damage-specific DNA binding protein 1 (DDB1) to trigger senescence, offering a novel Treg-targeted therapy [299]. Notably, immunoglobulin-like transcript 4 (ILT4) blocker PIR-B disrupts MAPK-ERK1/2-driven lipid accumulation in tumors, reversing T-cell senescence and boosting antitumor responses of responder T cells, highlighting lipid metabolism as a potential immunotherapeutic strategy [300]. Moreover, extracellular ATP (eATP) as an extracellular metabolism in TME induces stress-induced premature

senescence (SIPS) of T responder cells via purinergic receptor (P2 × 7) ion channel, though eATP may show opposite influence on the whole tumor and the intratumor myeloid subsets [301–303]. That is, again, specific P2 × 7 inhibitors targeting on T cells are needed.

B lymphocytes

Until now, research on B cells in the TME remains limited. Studies on senescence's effect on B cells in tumor-bearing human and animals mainly focused on subsets of them in peripheral blood. B1 cells (CD5 + CD19+), regarded as immature and innate B cells, which decline with aging, can transform into 4-1BBL + B cells (4BL cells) upon age. These cells activate GrB + CD8 + T cells via mTNFα-TNFR2/4-1BBL, enhancing tumor cell killing at a low-threshold stimuli [304, 305]. Another B cell subset, B7-DC+ (PD-L2/CD273) B cells, significantly augment the induction of both Th1 and Th17 cells [306]. Besides, B cells in TME may contribute to the cancer metastasis [307]. Notably, these results still need to be proved in TME and vivo.

Cancer-associated fibroblasts (CAFs)

As mentioned above, CAFs could secret cytokines which promote cancer progression. Paradoxically, CAFs can enhance drug sensitivity in some contexts [308]. Senescent CAFs create a cancer-favoring microenvironment via SASP factors through multiple pathways. p38 MAPK enhances breast cancer growth by senescent CAFs, and MAPK oral inhibitor CDD-111 can inhibit SASP expression secreted by senescent CAFs [259]. Another signaling pathway in both CAFs and breast cancer cells is TGF-β/connective tissue growth factor (CTGF). Its activation induces HIF-1α-driven metabolic changes, promoting autophagy and senescence in cancer cells but tumor-supportive senescence and autophagy in CAFs via lactate release [309]. This phenomenon once again emphasizes the value of specific targeted therapy. Phosphoinositide 3-kinase (PI3K)/AKT (PKB, protein kinase B)signaling mediates similar protumor effects in melanoma [310]. Besides, senescent CAFs upregulate fatty acid transport protein 2 (FATP2) in melanoma cells to increase the tumor's uptake of lipids, conferring drug resistance eventually, and this process could be reversed by FATP2 targeting [311]. Surprisingly, resveratrol counteracts senescent CAFs' protumor effects in melanoma, providing a treatment that may induce an anti-tumor hosting microenvironment [312]. Interestingly, poly ADP-ribose polymerase inhibitor (PARPi)-induced SASP in CAFs reduces the efficacy of PARPi, an targeted drug which has already been utilized in many types of solid tumors though with drug resistance in long-term use, but combining bepotastine, a H1-antihistamine, restores sensitivity via NF-κB suppression [313]. However, senescent CAFs exhibit heterogeneity even in tumors with identical primary organ but different cell type. For instance, lung large cell carcinoma, rather than adenocarcinoma or squamous cell carcinoma, uniquely induces CAFs senescence through paracrine, leading to the aggressive behavior of tumor [314]. In short, key pathways (p38 MAPK, PI3K/AKT) and SASP factors are central to senescent CAF-driven tumor remodeling across cancers.

The relationship between aging and tumor immunotherapy

Overall, the interplay between tumor immunotherapy and aging remains unclear, influenced by complex TME and varied immunotherapy types. Current research emphasizes efficacy and safety of immunotherapy in elderly patients versus younger cohorts and underlying molecular mechanisms. PD-1 inhibitors (cemiplimab, pembrolizumab) show efficacy and safety in the treatment of elderly, immunocompromised patients with locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC) and non-small cell lung cancer (NSCLC) [315, 316], while CAR-T therapy demonstrates effectiveness and low toxicity in elderly multiple myeloma patients [317]. Additionally, the type, frequency, and severity of immune-related adverse events (irAEs) from cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) or PD-L1 inhibitors are comparable across age groups, with patients > 75 years deriving similar benefits as younger individuals [318], corroborated in melanoma studies [242]. Similar findings have been observed with other forms of immunotherapy. For instance, age also does not affect outcomes of intravesical Bacillus Calmette-Guerin (BCG) therapy for non-muscle invasive bladder cancer (NMIBC) [319]. These findings highlight age-neutral efficacy of certain immunotherapies but underscore the need for deeper mechanistic exploration.

However, when classifying irAEs by severity and affected organ systems, differences emerge between elderly and younger patients. Elderly patients on anti-PD-(L)1 therapy for solid tumors experience higher overall incidence of grade ≥ II irAEs and multiple irAEs [203]. Moreover, combination therapies result in irAEs that differ between elderly and younger patients. In metastatic renal cell carcinoma (mRCC), elderly patients treated with nivolumab (monotherapy or combined with ipilimumab) show similar antitumor responses to younger patients but experience higher incidence of gastrointestinal irAEs [320]. Similarly, aged over 70 receiving camrelizumab combined with chemotherapy exhibit increased incidence of both all-grade and high-grade irAEs [321]. To solve this side-effect, IL-6 receptor (IL6R) blockade combined with PD-L1 inhibition was found to reduce irAEs in solid tumors [322], though the age-specific safety and effectiveness clinical data are lacking.

Moreover, to balance the response and the side-effect of immunotherapy, the implementation of a dosing strategy that is tailored to the individual patient's pharmacokinetics is also a commendable approach. Pembrolizumab administration utilizing this method has been proven to show promising clinical efficacy and manageable toxicity [323], but age-tailored trials remain pending. However, considering the complexity TME in them, it is still a strategy worth exploring. Interestingly, despite the lack of age-related differences in treatment efficacy, elderly genitourinary cancer patients over 75 years with irAEs exhibit improved survival [324], a phenomenon not reported in other cancer types, possibly reflecting the disease characteristics of genitourinary cancers. A recent study also reported lower all-grade irAE incidence in elderly solid tumor patients over 70 on anti-PD-(L)1 therapy [325]. This opposite finding has not been observed in previous studies and warrants further validation with larger sample sizes.

The efficacy of immunotherapy in elderly patients exhibits contradictions: while some studies show comparable outcomes across ages in some cancers, reduced responses are observed in others. For instance, elderly patients (> 80 years) with superficial bladder cancer respond poorly to BCG or IFN-α therapy [326]. Furthermore, anti-PD-1 therapy is less effective in elderly glioblastoma patients due to abundant PD-1-negative CD8 + CD28 – T cells with cytotoxic dysfunction [327]. Mechanistically, aged mice exhibit diminished NK cell infiltration, cytotoxicity, and maturation. This leads to impaired recruitment of dendritic cells (DCs) to tumor-draining lymph nodes (TDLNs), ultimately resulting in diminished activation of tumor antigen-specific CD8 + T cells and reduced efficacy of anti-PD-L1 therapy. Infusing young NK cells into aged mice restored immunotherapy response, enhancing T cell infiltration in TME following immunotherapy [328]. In addition to anti-PD-1/PD-L1, aging also compromises therapies including anti-CD4 mAb, endotoxin injection, anti-OX40 antibody and CTLA-4 blockade, linked to T cell exhaustion and dysfunction in TME [329–331]. Moreover, elevated Tregs in aged TME suppress CTLs, though CpG oligonucleotide (CpG-ODN) adjuvant combined with Treg depletion boosts immunity without inducing immune memory in aged mice [332]. Promisingly, L-arginine supplementation enhances PD-1 antibody efficacy in aged CT26 colon cancer models by promoting CTL infiltration, though this benefit is tumor-specific for absent in MC38 models, suggesting tumor heterogeneity, which requires further molecular investigation [333]. Nevertheless, this study provides valuable insights into mitigating the potential decline in immunotherapy efficacy due to aging.

To address age-related immunotherapy resistance, combining ICIs with epigenetic modulators to reverse immunosenescence shows preclinical promise. For example, decitabine plus anti–PD-1 sustains the activity of the activator protein-1 (AP-1) transcription factor JunD in CD8 + T cells, which usually reduces following PD-1 blockade therapy, counteracting immunosenescence and enhancing proliferation [334]. Besides, the subtype-selective HDAC inhibitor (HDACi) tucidinostat combined with anti-PD-1 suppresses NF-κB signaling in CD8 + T cells, mitigating senescence [335]. Furthermore, DNMT inhibitors (DNMTi) reduce pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ), alleviating immunosenescence and inflammation [336]. However, clinical trials evaluating these combinations are ongoing, leaving human efficacy uncertain [337]. Notably, some therapies pose age-specific risks: anti-CD40/IL-2 triggers fatal cytokine storms, consisting of TNF, IL-6, IFN-γ in aged mice via macrophages, driving liver injury, but co-administration of TNF antagonist etanercept rescues survival without compromising antitumor effects of the therapy [338].

The varied results may stem from organ/cell-specific differences in immunosuppressive molecule expression. While PD-1 inhibitors show comparable efficacy in young and aged melanoma mice, PD-L1 inhibitors perform worse in aged subjects. This could be attributed to elevated PD-L1 and CD80 levels in aged DCs, forming heterodimers that preserve CD80's co-stimulatory role while neutralizing PD-L1's immunosuppressive effect. Thus, PD-L1 blockade in aged mice might dissociate these heterodimers, reducing co-stimulation and paradoxically increasing immunosuppression [339].

It is encouraging to note that with the rising emphasis on the health of the elderly, a number of clinical trials about immunotherapy on the prognosis among the elderly have emerged in NSCLC [340–344], esophageal squamous cell carcinoma [345–349], mantle cell lymphoma [350, 351], myelodysplastic syndrome [352], though most remain in Phase II trials pending results. Promisingly, completed trials demonstrate positive safety and efficacy outcomes. Multicenter studies reveal elderly patients with relapsed/refractory large B-cell lymphoma (R/R LBCL) receiving CAR-T therapy achieve comparable overall remission (ORR), complete remission (CR), median overall survival (OS), and progression-free survival (PFS) to younger cohorts [353, 354].

In short, aging patients show comparable immunotherapy responses to younger counterparts, though safety varies by tumor type. Moreover, IL-6 blockade enhances ICI safety, while epigenetic drugs improve efficacy by reducing immunosenescence. Besides, adjuvant therapies (e.g., probiotics [355, 356], JAK inhibitors [357]) further augment ICIs. However, clinical validation in elderly populations remains limited.

Communications and conclusions

Immunosenescence, a complex physiological process marked by phenotypic and functional alterations in innate and adaptive immune cells and chronic low-grade inflammation [358], lacks definitive etiology. Notably, it is not exclusive to aging populations—some younger individuals exhibit immune decline predisposing them to infections or age-related disease. Besides, immunosenescence is also not universal in aging: centenarians often retain robust immune systems, suggesting healthy immunity may underpin longevity [359].

In this review, we identify key hallmarks of immunosenescence as genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, autophagy defects, mitochondrial dysfunction, cellular senescence, HSCs myeloid bias, altered inter-cellular communication, chronic inflammation, and gut dysbiosis. — act as interconnected drivers of immune decline. For example, mitochondrial dysfunction promotes chronic inflammation by mtDNA leakage and ROS accumulation, which activates the cGAS-STING pathway. Besides, gender differences in immunosenescence are also mentioned in our review, with males showing higher pro-inflammatory cytokines (IL-6, TNF-α) and senescent T cells, both of which may explain why women live longer than men [360]. Notably, the development of epigenetic clocks (e.g. IntrinClock) has provided new tools for assessing biological age, but their utility in tracking immune cell changes requires refinement. While our framework prioritizes intervention-validated drivers (e.g., mitochondrial dysfunction, autophagy), we acknowledge that certain features (e.g., proteostasis loss) exhibit strong associations but require further mechanistic interrogation. Future studies combining genetic models (e.g., conditional knockouts) and age-stratified clinical trials will solidify causal links. Besides, recently there has been study indicating the interaction between altered extracellular matrix and immunosenescence [361, 362]. Considering the altered extracellular matrix has already been concluded into aging hallmarks [363], researches about the relationship between extracellular matrix and aging should also go further.

The TME has been a hot topic recent years with a raise of immunotherapy. In the past, relationship between aging and TME hasn't received enough attention, which may lead to the therapy failure when converting animal trial results into clinical trial efficacy. That's partly because most of the animal trials utilized young mice before, while tumor is more common in aging population with immunosenescence [15, 364]. In this review, alterations of TME brought by senescence are summarized. During the last twenty years, this field gained truly rapid development. Results show that TME in elderly provide a immunosuppressive environment to promote tumor growth, though heterogeneity of mechanism lies in almost every phase of tumor initiation and progression in elderly, which exists in different tissues and organs; reverse function of the same SASP on tumor and TME, etc [256, 309, 314, 365]. Such heterogeneity necessitates cell- or organ-specific biomarkers for targeted therapies or identification of conserved pathways, including MAPK/STAT1/3 in senescent T cells [258]. Despite progress, TME-targeting approaches remain largely preclinical [366, 367], highlighting the urgent need for elderly-inclusive clinical trials addressing age-related physiological vulnerabilities.

Besides, there are some immune cells whose function in TME when senescence hasn't been depicted yet. Autologous NK infusion effectively alleviates T cell senescence and exhaustion and suppresses SASP components, though mechanisms remain unclear [368]. B cell senescence is under-researched due to their oncogenic potential and frequent classification under tumor cell senescence [369]. Further exploration still needs on these unexplained cells for better understanding of TME senescence and more treatment of tumor. Fortunately, although the immune system of aging tumor patients is often weakened by the presence of immunosenescence, PD-1 inhibitors show comparable efficacy in older solid tumors, but CD8 + CD28 – T-cell accumulation may drive glioma resistance. In addition, current studies still seem to be inconclusive regarding the incidence of irAEs. Debate persists regarding increased irAE incidence in elderly patients, with some studies contradicting this risk. The incidence of irAEs in elderly cancer patients may require tumor type-specific evaluation. Furthermore, combination treatment strategies (e.g., L-arginine to enhance CTL infiltration) or engineered cytokines (GIFT-7 activated DCs) in senescent patients show promise for improving outcomes.

In the past, it was widely believed that the immunosenescent environment in aging tumor patients showed pro-tumorigenic features. However, recent studies have shown that systemic immune dysregulation due to aging presents dynamic compensatory features. Subsets of aged CD8 + T cells acquire NK-like cytotoxicity to inhibit metastasis, though their in vivo relevance remains unconfirmed. This reveals the aging immune system's 'double-edged sword' effect. In short, given the impact of ageing on systemic immunity, the TME, and immunotherapy, future treatments for elderly oncology patients should aim to restore anti-tumor immune activity while suppressing chronic inflammation by targeting aging-related immunosuppressive pathways, such as the STING/cGAS pathway and SASP modulation. Meanwhile, optimizing ICIs with aging hallmarks, such as combining TLR8 agonists or metabolic regulators could enhance efficacy. Furthermore, it is imperative to

ameliorate the immunosuppressive state of the ageing TME, for instance, by remodeling dendritic cell (DC) function with CD40 agonists to enhance antigen presentation and improve the cytotoxicity of tumor-infiltrating T cells. Finally, metabolic interventions (Spermidine, NMN) or dietary adjustments may reverse immune senescence and rejuvenate antitumor responses.

Recent advancements in single-cell technologies have significantly enhanced our understanding of immunosenescence and its implications for therapy. For example, a study utilizing scATAC identified chromatin regulators of PD-1 blockade therapy-responsive T cell subsets and revealed the differentiation trajectories of these subpopulations in the TME [370]. This may provide a potential therapy target on regulation of these subsets to increase the effect of immunotherapy. An integrated multi-omics database on immunosenescence, which was built using AI models to provide information on the changes associated with aging in the dynamics of immune cells and cytokine levels, as well as the single-cell sequencing, transcriptomics, and epigenomics data are expected to pinpoint therapeutic targets [371]. Furthermore, recent innovations include a single-cell immunosenescence clock using PBMC-derived myeloid and lymphoid populations, overcoming prior biases on immune cell type and improving immunosenescence prediction after vaccination. However, scaling these models with larger, more diverse datasets remains critical for robust clinical translation [372].

In the context of immunosenescence, single-cell sequencing has revealed significant alterations in T cell populations. T cells exhibit significant subpopulation differentiation and functional evolution in the spleen. Recent study not only identified 11 age-dependent dynamic subpopulations of $CD8^+$ T cells but also discovered a unique pro-inflammatory aging subpopulation within $CD4^+$ T cells. These cells drive immunosenescence through abnormal cytokine secretion [373–376]. Besides, a cross-organ single-cell analysis indicates that the lung is highly susceptible to aging. In lung tissue, the proportion of IL-17-expressing γδT (γδ17) cells increases with age, recruiting CD62L-low pro-tumor neutrophils. These neutrophils suppress the stemness and tumor-killing functions of $CD8^+$ T cells in aged male mice [377, 378]. This organ-specific immunosenescence characteristic provides a mechanistic explanation for the increased susceptibility to respiratory infections and tumor metastasis in elderly individuals.

Single cell ATAC-seq has also been used more and more recently to connect T cell changes in immunosenescence with epigenetic alterations. A study employed ATAC-seq to ascertain that chromatin accessibility diminishes in elderly naïve CD8 + T cells due to diminished NRF1 binding, culminating in impaired respiratory chain gene transcription and oxidative phosphorylation capacity, which indicates the NRF1 may be identified as a potential target for interventions aimed at decelerating CD8 + T cell senescence and restoring function [379]. Moreover, recent thymic emigrant (RTE) T cells, decreasing because of the thymic involution during immunosenescence, are distinguished by the expression of SOX4, IKZF2, and TOX and CD38 protein, as well as surface CD38 high expression universally identifies CD8 + and CD4 + RTEs. This means CD38 ++ RTE T cells may provide insights into thymic health, thus better assessing the immunosenescence [380].

Moreover, the characterization of inflammation and oxidative stress at single-cell resolution has underscored their roles as core features of immunosenescence. Aging-related transcriptional features prevalent in the hematopoietic immune system (HIS) reveal that immune cells in the spleen and bone marrow highly express inflammatory mediators and oxidative stress genes, forming the cellular basis for chronic low-grade inflammation [381, 382]. Monocytes from severe COVID-19 patients exhibit accelerated aging, confirming the amplifying effect of infection stress on immunosenescence [383].

Interestingly, the aging process of the immune system exhibits significant gender dimorphism. At the cellular level, the proportion of plasma cells in peripheral blood is significantly higher in females than in males, while the proportion of NK cells is lower. This difference becomes more pronounced with age, directly influencing the differentiation of anti-infection and anti-tumor capabilities between the sexes [384]. In elderly females, the number of memory T cells (especially the $PD\text{-}1^+CD4^+$ subpopulation) decreases in an age-dependent manner, while males maintain relatively stable levels [385]. In animal models, aged female mice exhibit increased spleen weight but reduced spleen cell count per unit weight, revealing gender-specific degradation of the spleen microenvironment [386].

The underlying mechanisms of these cellular differences involve gender differentiation in immune signaling pathways. T cell senescence in females is closely associated with excessive IL-7 signaling and abnormal N-glycan branching, leading to accelerated T cell dysfunction [387]. Regulation of neuroimmune also exhibits gender differences. Microglia undergo specific transcriptional and epigenetic reprogramming during senescence, which affects the progression of neurodegenerative diseases [388].

Sex-specific differences in immunosenescence profoundly influence tumor immune surveillance efficacy. Male individuals experience faster tumor progression due to impaired $CD8^+$ T cell effector function and stem cell-like properties, leading to weakened antitumor immune responses [389, 390]. Sex hormones mediate this

process through three mechanisms: regulating immune cell infiltration in the TME, altering cytokine secretion profiles, and modulating immune checkpoint molecule expression, ultimately indirectly weakening immune surveillance [391, 392].

Although current studies have made significant progress in resolving the interaction between immunosenescence and tumors, many key scientific questions remain to be explored in depth. First, while T cell and macrophage senescence is well studied, B cell and γδ T cell dynamics in aged TME remain unclear, necessitating single-cell multi-omics for spatiotemporal resolution. Secondly, the integrated regulation of the neuro-immune-metabolic axis is another area in need of a breakthrough: how does dysregulation of the hypothalamus-thymus axis drive thymic atrophy and weaken anti-tumor immunity through hormonal signals (e.g., melatonin, CRH)? Can targeting neuroendocrine pathways reverse the immunosuppressive properties of TME? These questions require a combination of gene editing and in vivo imaging techniques for mechanistic resolution. Thirdly, with much attention on the tumor immune status of elderly patients, should people also pay attention to the influence of the patients' own metabolic conditions and aging-related factors on both the immune system and tumor aging? In addition, current murine systems poorly replicate human immune senescence heterogeneity. Humanized senescence-tumor-like organ- or patient-derived xenograft (PDX)-based models could better mimic the pathological features and drug responses of senescent TME. Finally, the integration of artificial intelligence and multi-omics provides new opportunities for precision medicine: by integrating epigenetic, metabolomic and immunomic data through machine learning algorithms, dynamic models can be constructed to predict immunotherapy response in elderly patients, though clinical validation in large cohorts remains pivotal. These advances could decode immunosenescence mechanisms and enable targeted strategies to counteract immunosenescence, promoting both tumor control and "healthy aging."

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

Declarations

Competing interests
The authors declare no competing interests.

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