

The ageing immune system as a driver of systemic ageing

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Abstract

Older individuals exhibit distinct biochemical and functional changes in their immune cells that can lead to chronic inflammation, reduced immunity to pathogens and organ dysfunction. Immune cells from older individuals acquire dysfunctional immunosenescent phenotypes that are classified as inflammatory, exhausted or senescent. Key molecular mechanisms, commonly described as hallmarks of ageing, drive the development of these phenotypes through both cell-autonomous and non-autonomous mechanisms. Importantly, the ageing immune system can drive multi-organ dysfunction and systemic ageing, suggesting that improving immune function in older individuals could have significant health benefits. Here, we review the effects of ageing on various immune cell subsets in mice and humans. We describe the molecular mechanisms that drive these functional changes and their effects on both lymphoid and non-lymphoid organs. We also discuss therapeutic approaches to improve the function of the ageing immune system to increase resilience and extend healthspan.

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Introduction

The complex combination of molecular changes in the ageing immune system contributes to the dysfunctional crosstalk among organ systems in chronologically older individuals. The human immune system is composed of 1.3 trillion cells that make up lymphocyte and myeloid compartments¹. As a result of the required self-renewal capacity, responses to diverse signalling pathways following pathogen exposure or the need to elicit an organ-wide immune surveillance, immune cells are exceptionally dynamic and exhibit differing degrees of susceptibility to cellular stress. Importantly, the changes in immune function with age are more than just a consequence of chronological ageing as they also contribute to driving the systemic ageing process (Fig. 1).

The immunological theory of ageing suggests that the development of a dysfunctional immune system over time is a direct driver of the pathology associated with ageing^{2,3}. The dysfunctional ageing immune system is widely characterized by an inflammatory or exhausted phenotype as well as by a still poorly characterized senescent-like phenotype of immune cell subsets (Box 1). Several lines of recent evidence support the immunological ageing theory and highlight the consequences of the senescent immune cell phenotype, including age-related organ damage. For example, in a mouse model, selectively increasing DNA damage in immune cells through targeted deletion of a DNA repair complex resulted in immune cells with a senescent-like phenotype⁴. This targeted acceleration of damage to immune cells led to immune dysfunction, increased tissue damage and a shortened lifespan⁴. Interestingly, despite the induction of DNA

damage in all immune cells, short-term treatment with the senotherapeutic rapamycin improved immune function and reduced markers of senescence⁴. This study, along with others investigating the impact of altered epigenetic regulation⁵ and mitochondrial function^{6,7}, mechanistically tested the role of cell-autonomous immune dysfunction during ageing. These studies strongly suggest that cell-intrinsic changes contribute to systemic ageing through non-cell-autonomous pathways (Fig. 1). Thus, approaches that aim to improve immune functionality during ageing by targeting these pathways should extend the period of healthy ageing.

Ageing in primary lymphoid organs is marked by thymic involution and declining haematopoiesis. This shift favours myelopoiesis over lymphopoiesis and alters the balance between innate and adaptive immunity. Consequently, the adaptive immune system declines in both quality and quantity, with fewer naive lymphocytes and more memory cells, reducing immune diversity and responsiveness in older individuals^{8,9}. The deterioration of immunity can lead to organ dysfunction owing to altered interaction between aged immune cells and stromal cells, disruption of tissue architecture and increased fibrosis, myeloid cell-derived inflammation, and lymphocyte infiltration (Fig. 1). These pathological changes are likely driven by the interconnected processes of immunosenescence, inflammaging and cellular senescence of the ageing immune system (Box 1). In this Review, we highlight age-associated changes in immune cell phenotypes and functions (Box 2), the cell-intrinsic mechanisms that are altered with age, and the consequences on systemic ageing. We also discuss the development of new approaches for

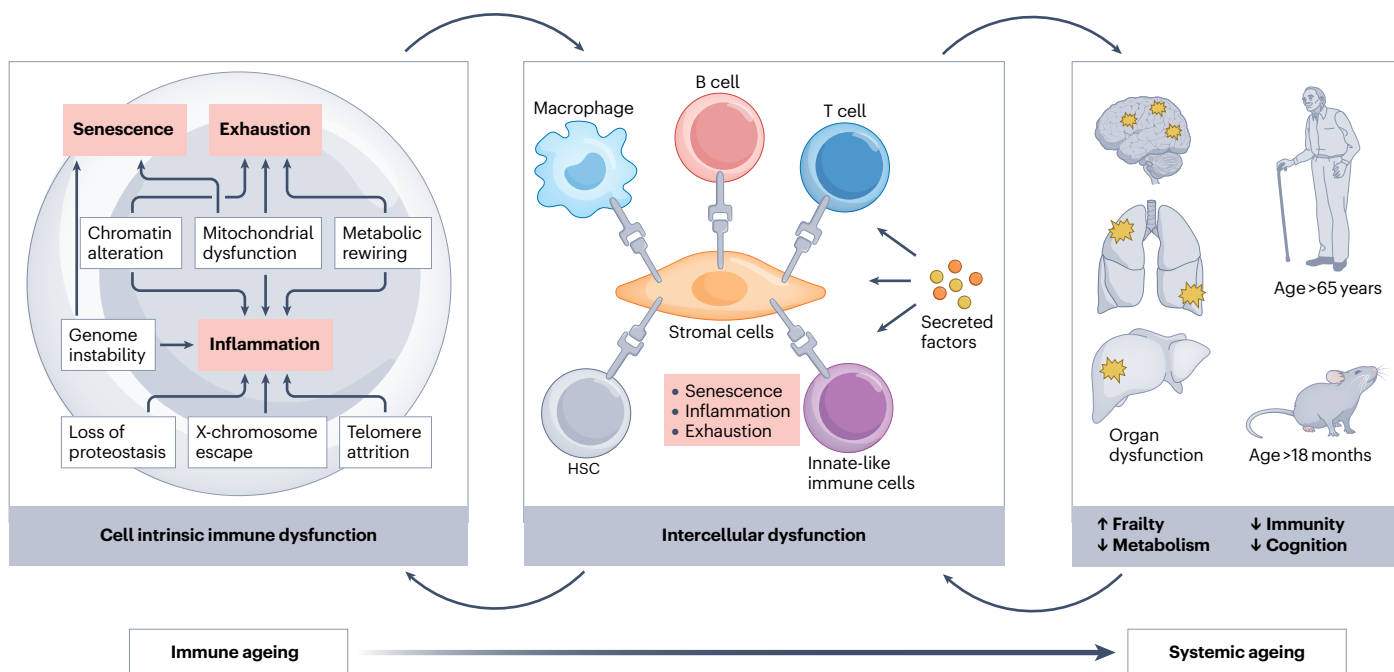


Fig. 1 | Contribution of immune ageing to systemic ageing. Age-associated changes in immune function contribute to the overall systemic ageing process. Immune ageing is characterized by the acquisition of defined dysfunctional phenotypes, including inflammatory, senescent or exhausted cell states. These dysfunctional phenotypes are primarily driven by cell-intrinsic alterations, such as chromatin alterations, mitochondrial dysfunction, metabolic rewiring, genome instability, loss of proteostasis, X-chromosome escape and telomere attrition (discussed further in the ‘Intrinsic immune ageing’ section

of the main text). Moreover, altered intercellular interactions between aged immune cells and stromal cells are a key feature of immune ageing, which is discussed throughout this Review. Immune ageing promotes systemic ageing, including dysfunctional organ systems that lead to increased frailty, altered metabolism, declining immunity and reduced cognition. Here, we define ‘aged’ immune cells as those from hosts at the later stages of life (for mice, >18 months; for humans, >65 years). HSC, haematopoietic stem cell.

Box 1 | Definitions for key terms and concepts related to ageing and the immune system

Chronological and biological age: Chronological age refers to the number of years an individual has lived, while biological ageing reflects the functional state of cells and organs, influenced by genetic, environmental, and lifestyle factors. Individuals with the same chronological age may differ significantly in biological age, which is a better predictor of healthspan and disease risk.

Immune ageing: This refers to the molecular and biochemical changes that occur in immune cells with age, leading to functional differences in immune cells from chronologically young or old individuals. These age-associated changes include DNA damage, telomere attrition, mitochondrial dysfunction, epigenetic alterations and dysfunctional proteostasis, all of which contribute to immune dysfunction with age.

Immune ageing clocks: Recent advances in deep learning and longitudinal omics approaches enabled the development of ageing clocks — tools that estimate biological age based on molecular features of immune cell subsets. Through a multilayered omics approach to characterize peripheral blood mononuclear cells, several immune ageing clocks have been introduced (for example, iAge¹¹, IMM-AGE¹² and sc-ImmuAging¹³). These immune ageing clocks have shown promise in predicting multimorbidity, immunosenescence, frailty, cardiovascular ageing, and individual responses to infection and vaccination¹².

Immunosenescence: This term describes the immune dysfunction that is seen with age. It is characterized by marked remodelling of lymphoid organs, reduced production of naive lymphocytes, accumulation of memory cells and decreased immune surveillance. These changes contribute to increased infection risk, poor vaccination efficacy and age-related diseases. Immunosenescence also reduces the ability of the immune system to clear senescent non-immune cells, resulting in increased levels of inflammaging, loss of tissue homeostasis and reduction in tissue function.

Inflammaging: This refers to the chronic, low-grade, systemic inflammation that is seen in older individuals and that occurs

independently of other co-morbidities. Chronic low-level activation of pattern-recognition receptors, including Toll-like receptors and NOD-like receptors. These pattern-recognition receptors are activated by persistent exposure to pathogen-associated molecular patterns (bacterial and viral components) and damage-associated molecular patterns (components released from stressed, damaged or dying cells). Activation of Toll-like receptors and NOD-like receptors by pathogen-associated molecular patterns and damage-associated molecular patterns contribute to inflammaging by triggering innate signalling pathways, such as the NF- κ B pathway, leading to secretion of inflammatory cytokines and chemokines. Many of these pro-inflammatory secreted factors overlap with components associated with the senescence-associated secretory phenotype (SASP).

SASP: This term describes a cell state expressed by senescent cells (see 'Cellular senescence') that includes the ability to secrete a wide range of pro-inflammatory cytokines, chemokines, proteases, bioactive lipids, inhibitory molecules, extracellular vesicles, metabolites and other factors. Ultimately, these secreted phenotypes promote chronic inflammation, tissue pathology and secondary senescence.

Cellular senescence: A cell state that is driven by multiple types of stressors, including replicative and genotoxic stress and oxidative damage. Senescence is defined by exit from the cell cycle and is accompanied by distinct cellular changes, including nuclear architecture alterations, increased expression of SASP factors, and elevated senescence-associated β -galactosidase activity. Increased expression of the cell-cycle-dependent kinase inhibitors p16^{Ink4a} and p21^{Cip1} are commonly used to identify senescent cells.

Systemic ageing: The pathophysiology of organs in older individuals that is distinct from that seen in younger individuals. These changes are associated with increased risk for disease and declining function, which can be represented by measuring changes in secreted factors, qualitatively assessing organ architecture, or quantifying the frailty index or decreased resilience to pathogens or stress.

immune rejuvenation to increase resilience and extend healthspan. We primarily discuss recent findings from mouse models unless stated otherwise. For a more in-depth discussion of age-related immune changes in humans, we refer readers to previous studies^{10–14}.

Age-related changes in HSCs

Multipotent haematopoietic stem cells (HSCs) sustain adaptive and innate immunity through lifelong self-renewal and differentiation into myeloid and lymphoid lineages. Ageing, however, leads to HSC exhaustion, which is marked by increased myelopoiesis and an increase in chronic diseases. For example, the bias towards myeloid cell production with age promotes tumorigenesis by increasing the systemic levels of myeloid cell-derived inflammatory cytokines¹⁵. Conversely, the pathogenesis of age-related diseases, such as myocardial infarction, can further exacerbate myelopoiesis, resulting in a vicious cycle with elevated levels of inflammatory myeloid cell infiltration and tissue

dysfunction¹⁶. Notably, transplantation of HSCs from young mice into aged mice improves physical performance, restores lymphopoiesis and rejuvenates immunity in the aged recipients, which implicates the cell-autonomous ageing features of HSCs¹⁷. CD150, a cell surface glycoprotein, is a critical marker of age-associated HSCs^{17,18}. CD150⁺ HSCs accumulate with age, exhibit increased myeloid-biased output and show ageing-associated epigenetic signatures, while CD150⁻ HSCs retain their balanced differentiation potential during ageing^{17,18}. Middle-aged mice that receive a transplant of aged CD150⁻ HSCs show an extended healthspan and lifespan compared to mice that receive a transplantation of CD150⁺ HSCs¹⁷. Similarly, antibody-mediated depletion of CD150⁺ HSCs improves immune function in aged mice¹⁸. Mitochondrial dysfunction, along with other undefined factors, have been shown to contribute to cell-intrinsic ageing of HSCs^{19–21}.

Whether there is a corresponding decline in lymphopoiesis is an ongoing area of interest²². A Kit^{low} subset of HSCs with greater lymphoid

Box 2 | Productive immunological functions supporting tissue homeostasis

The immune system is required for defence against foreign material, pathogens and abnormal cells. Tissue-resident immune cells support functional stromal cells, sustain appropriate tissue remodelling and functionality, and regulate the balance of pro-inflammatory and anti-inflammatory factors in the tissue microenvironment. Productive immune responses are commonly measured in mouse models or ex vivo assays with primary immune cells. To interrogate organ function, research typically combines non-terminal whole-body analysis with terminal organ harvests that assess specific aspects of organ functionality. A few general examples are provided here.

Changes in metabolism can be assessed with an insulin tolerance test, glucose tolerance test and measurements of body weight and body composition. Neurological and physical changes can be examined using the grip strength test, pole test, rotarod test and the open field test. Non-invasive biomarkers measured from the blood include indicators of tissue damage (for example, liver enzymes and cardiac troponin), inflammation (for example, cytokines) or disease-associated proteins (for example, tau and amyloid- β). In parallel, organ harvest can be used to analyse single cells or fixed to preserve the architecture features. A wide range of analyses on single cells or fixed tissues provide insight into epigenetic, transcriptional or proteomic changes, offering evidence of their phenotype and functionality changes.

The ideal functional test uses a stimulus that induces a known immune cell response. The combination of these experimental approaches supports the idea that the ageing immune system is marked by inflammatory, exhausted or senescent features, which collectively promote organ dysfunction. Table 1 provides a list of the dysfunctional changes within specific organs that have been described to occur as a result of ageing of the immune system.

potential has higher activity of lymphoid-specifying transcription factors and exhibits a decrease in population size with age²³. Transplantation of Kit^{low} HSCs from young donors into middle-aged hosts led to thymic reconstitution and restoration of lymphoid progenitors, potentially improving adaptive immunity in the recipients²³. Moreover, inhibiting clusterin, which promotes excess mitochondrial fusion, oxidative phosphorylation and reactive oxygen species (ROS) production in HSCs, restored their differentiation potential towards lymphopoiesis and improved physical function (Box 2) in old mice²⁴.

Clonal haematopoiesis of indeterminate potential (CHIP) is a condition characterized by a selective expansion of mutated progeny cells that show hyperinflammatory activity. CHIP is linked to adverse outcomes and age-related diseases in older individuals, with *TET2* (encoding TET2, a dioxygenase important for regulation of genomic methylation) and *DNMT3A* (encoding DNA methyltransferase 3A (DNMT3A)) being the most frequently mutated genes^{25–27}. Given that TET2 and DNMT3A modulate DNA methylation, maintenance of epigenetic regulation appears to be crucial for CHIP. Patients with cardiovascular disease who have TET2 CHIP mutations benefit from IL-1 β neutralization, suggesting that IL-1 β is a major effector of CHIP-driven cardiovascular disease⁵. In a DNMT3A heterozygous loss-of-function mouse model, there was clonal expansion of myeloid and lymphoid

lineage cells along with increased bone marrow osteoclast precursors as well as osteoclastogenic macrophages in the periphery²⁸. When mutant *DNMT3A* bone marrow was transplanted into wild-type hosts, it exacerbated periodontitis, IL-17-driven inflammation, and arthritis²⁸. Intriguingly, rapamycin treatment suppressed CHIP-driven inflammation²⁸, suggesting that a portion of the CHIP-transplanted cells may acquire a senescent-like phenotype. Of note, CHIP is less common in centenarians²⁹. By contrast, a recent study reported a beneficial role of CHIP in Alzheimer disease, primarily through its effects on brain myeloid population via increased infiltration and enhanced phagocytosis^{30,31}. This may suggest a disease context-specific or tissue-specific role for CHIP in age-related diseases. It is important to note that HSCs from aged mice do not display the same loss of clonal diversity that is seen in the human haematopoietic compartment with ageing³². Instead, certain HSC clones in mice can become larger and more numerous following perturbations such as pathogen exposures³², indicating that the selection process of HSCs in mice is similar to that seen in humans and is primarily driven by environmental challenges³².

Beyond the intrinsic HSC ageing, the bone marrow microenvironment undergoes inflammatory remodelling that disrupts HSC function and commonly leads to myeloid bias with age. Accumulating bone marrow adipocytes and the resulting close proximity between adipocytes and HSCs leads to a decrease in HSC number, self-renewal capacity and elevated inflammatory cytokine release³³. Levels of neutrophil-derived semaphorin 4a in the bone marrow decline with age, leading to the expansion of myeloid-biased HSCs and increased myelopoiesis mediated by AP-1 family transcription factors³⁴. Furthermore, aged bone marrow plasma cell populations expand and secrete IL-1 β and tumour necrosis factor (TNF), which activate bone marrow stromal cells and drive myeloid skewing³⁵. Depleting plasma cells or blocking IL-1 α , IL-1 β and/or TNF reverses the age-associated bias in myelopoiesis³⁵. Replacing aged bone marrow stromal cells with skeletal stem cells from young mice shifts differentiation away from a myeloid bias, which underscores the influence of the aged bone marrow niche on haematopoietic ageing³⁶.

Age-related changes in adaptive immune cells

The adaptive immune system comprises lymphocytes that are responsible for generating antigen-specific responses and immunological memory. Lymphocytes undergo numerous age-related changes that depend on their cell subset type, location and pathogen exposures^{37–42}. As the ageing of mature CD4⁺ and CD8⁺ T cells has been extensively reviewed by multiple groups, we direct readers to previous reviews for a more comprehensive discussion on this topic^{9,37–39}. Here, we highlight some key recent findings, focusing on differences in epigenetic memory, altered mitochondrial function and the induction of exhaustion with T cell ageing^{6,7,43–47}.

CD4⁺ T cells

CD4⁺ T helper cell subsets show differences in their differentiation, mitochondrial bioenergetics, redox imbalance and cytokine production with advancing age^{48–50}. In naive T cells, expression of HELIOS, a critical transcription factor involved in CD4⁺ T cell differentiation, is reduced in older individuals (that is, those aged 65 and over)⁴³. Despite blunted T cell receptor (TCR) signalling in naive CD4⁺ T cells from older individuals, the stimulation of these cells results in accelerated remodelling of the epigenome and increased effector T cell differentiation. This is driven by a reduction in HELIOS expression leading to early upregulation of CD25 and increased STAT5 activation⁴³. Inhibition of STAT5 or CD25 restored the epigenetic landscape, which highlights

the reversibility of this state⁴³. CD4⁺ T cells also exhibit compensatory alterations for age-related naive T cell loss by optimizing IL-7 signalling, which supports peripheral homeostatic proliferation⁵¹. This process is mediated through increasing levels of PREX1, a guanine nucleotide exchange factor that promotes STAT5 activity, representing an example of a compensatory adaptation during ageing⁵¹.

A causal role for impaired T cell mitochondrial function in ageing-associated changes in physiology was demonstrated by CD4⁺ T cell-specific deletion of the mitochondrial transcription factor TFAM. This resulted in a senescent-like phenotype in CD4⁺ T cells that also drove systemic features of ageing, including metabolic, cognitive and physical decline, chronic inflammation, and peripheral tissue senescence⁶. Importantly, the TFAM-deficient CD4⁺ T cell-driven ageing phenotype was preventable as the deletion-induced decline in the ratio of NAD⁺ to NADH was alleviated by supplementation with a NAD⁺ precursor, resulting in less tissue damage and restoring physical performance⁶. A reduction in lysosomal function in aged CD4⁺ T cells impairs mitochondrial quality control and leads to the extracellular release of mitochondrial DNA (mtDNA), which acts as a damage-associated molecular pattern (DAMP) to trigger inflammation⁵². Interestingly, mitochondrial transfer from healthy fibroblasts to aged CD4⁺ T cells enhances aerobic metabolism and reduces ROS, which improves T cell activation and proliferative capacities⁵³. Together, these studies highlight critical cell-intrinsic mechanisms underlying CD4⁺ T cell dysfunction that could be therapeutically targetable.

CD8⁺ T cells

Cytotoxic CD8⁺ T cells confer defence against infections and mediate immune surveillance in tissues through granzyme-dependent and perforin-dependent mechanisms. However, excessive TCR signalling or cytokine-mediated stimulation leads to an increase in the number of memory T cells and virtual memory T cells that show an exhausted phenotype, resulting in compromised cytotoxic T cell responses with age^{39,54,55}. Exhausted CD8⁺ T cells are characterized by increased expression of inhibitory receptors, such as PD1, elevated secretion of inflammatory factors, and reduced effector function³⁹. Age-associated CD8⁺ T cells from older individuals fail to express granzyme B (GZMB), a serine protease involved in cytotoxic activities, but instead secrete granzyme K (GZMK), which induces DNA damage and promotes the expansion of senescent cell populations and upregulation of senescence-associated secretory phenotypes (SASPs)⁵⁶ (Box 1). Similarly, the shift from GZMB⁺ to GZMK⁺ cells with age is observed in healthy older humans⁵⁶. GZMK⁺ T cells are also implicated in airway inflammatory diseases, suggesting that they could be cellular therapeutic targets⁵⁷. CD8⁺ T cells can also reside permanently in non-lymphoid tissues where acquisition of an age-dependent, senescent-like inflammatory phenotype can drive tissue pathology. However, tissue-resident memory T cell numbers are reduced with age, and this is associated with the expression of bifunctional apoptosis regulator (BFAR)⁵⁸. A BFAR-specific inhibitor was able to restore resident memory T cell generation and protect against tumorigenesis with ageing⁵⁸.

The cytotoxic capacity of CD8⁺ T cells in targeted clearance of senescent cells also declines with advancing age. Global deficiency in perforin, which is required for cell lysis by CD8⁺ T cells, results in increased senescent cell accumulation and accelerated ageing⁴⁵. Senescent cells can also actively avoid clearance, for example, by upregulating PDL1 to inhibit the activity of PD1-expressing cytotoxic cells⁴⁶. Antibody-mediated blockade of the PD1–PDL1 pathway restores immune-mediated clearance of senescent cells, reducing senescence

and alleviating age-related pathologies such as hepatic fibrosis and steatosis in aged mice⁴⁶. Moreover, PD1 blockade improves survival during pathogen exposure in aged mice through enhanced cytotoxic capacity of CD8⁺ T cells⁴⁷, reiterating the potential of targeting T cell functionalities for improved immune resilience during ageing.

B cells

With ageing, splenic B cells show notable changes, such as greater clonal expansion, telomere shortening and promoter hypermethylation, which impairs immune robustness, with reduced antibody production seen in response to infection and vaccination^{40,42,44}. Follicular B cells that are essential for memory B cells and long-lived antibody-secreting plasma cells are outcompeted by age-associated B cells (ABCs), which increase in number in a B cell activating factor (BAFF)-independent manner⁴². Chronic inflammation supports the increase in ABCs as *Tlr7* and *Nlrp3* deficiency reduce ABC numbers in mouse models of ageing^{42,59}. Notably, X-chromosome inactivation escape promotes *Tlr7* overexpression, supporting the development of autoimmunity⁶⁰. This mechanism may drive age-related sex dimorphism, as Toll-like receptor 7 (TLR7) signalling promotes a female-specific B cell accumulation, leading to increased production of autoantibodies and inflammatory cytokines⁴². Follicular B cells require mitochondrial remodelling upon antigen encounter to facilitate antigen presentation and subsequent germinal centre reactions⁷. B cell-specific mitochondrial dysfunction mediated by TFAM deletion impairs germinal centre reactions and contributes to the expansion of ABCs⁷.

Recently, an expanded population of CD21⁺CD23⁺CD24⁺ age-associated clonal B cells (ACBCs) was identified. Originating from ABCs, ACBCs exhibit reduced interferon signalling, high clonality driven by MYC and altered DNA methylation in promoter regions, and infiltration into the periphery⁴⁴. An increase in circulating ACBCs, marked by larger sizes, positively correlated with mortality in aged mice⁴⁴. In the peritoneum, aged innate-like B cells become aberrantly activated in a T cell-independent manner, undergo clonal expansion and develop a senescent-like phenotype⁶¹. While common age-associated dysfunctions, such as mitochondrial dysfunction and altered differentiation profiles, are observed in both T cells and B cells, only T cell dysfunction has been shown to be reversible.

Age-related changes in innate and innate-like immune cells

Innate immune cells and innate-like lymphocytes are diverse cell populations that originate either during embryonic development or from bone marrow precursors throughout life. Their functions are largely centred around tissue surveillance, maintenance of homeostasis and acute responses to pathogens. It is possible to reduce inflammatory factors derived from aged macrophages by inhibiting specific receptors or signalling pathways. For example, targeting the NLRP3 inflammasome, a key regulator of IL-1 β and IL-18 secretion, mitigates metabolic dysfunction with age⁶². To date, only macrophages have been shown to adopt a more 'youthful' phenotype, which is characterized by enhanced phagocytic activity and reduced pro-inflammatory cytokine production. Whether age-related changes in most innate or innate-like immune cells can be reversed remains largely unclear.

Macrophages

Macrophages are phagocytic cells that are essential for immune surveillance, antigen presentation and tissue homeostasis⁶³. Their ability to phagocytose apoptotic cells, a process termed efferocytosis,

is critical for effective immune surveillance and tissue homeostasis. However, with ageing, macrophages show impaired phagocytosis and an elevated inflammatory phenotype⁶⁴. Such macrophages fail to clear apoptotic cells via MerTK-mediated efferocytosis, leading to the accumulation of apoptotic bodies⁶³. Macrophages from older individuals also exhibit elevated ROS levels, which promote ADAM17-mediated MerTK cleavage, impairing efferocytosis and increasing tissue inflammation⁶⁵. In addition, necroptotic cells release extracellular DNA that further skews macrophages towards an inflammatory phenotype; however, suppressing ADAM17 or ROS restores efferocytosis and reduces inflammation⁶⁵. Notably, the transcription factor KLF4 confers circadian gene regulation in macrophages from young mice, but its age-dependent loss of rhythmicity compromises phagocytic function, highlighting the importance of circadian regulation in affecting macrophage function with ageing⁶⁶.

Pathogen-associated molecular patterns and DAMPs also drive inflammaging via their effects on macrophages, and this is a well-recognized feature of ageing⁶³. For example, adipocyte-expressed SPARC (secreted protein acidic and rich in cysteine) is a DAMP that binds to TLR4 on macrophages, leading to increased interferon-stimulated gene expression in older mice⁶⁷. Adipocyte-specific deletion of SPARC in mice improved physical performance, extended lifespan and enhanced tissue homeostasis in older mice, with a reduction in inflammatory macrophages⁶⁷. This pathway illustrates how the local crosstalk between non-immune and immune cells in a tissue is crucial for regulating inflammaging.

Adoptive transfer of macrophages from old mice to a young host promoted tissue senescence in both lymphoid and non-lymphoid tissues⁶⁸. This ability to promote secondary senescence was driven by the transferred macrophages secreting extracellular vesicles, which contained microRNAs that inhibit PPAR α ⁶⁸. This induction of secondary senescence was prevented by a PPAR α agonist (fenofibrate) with senotherapeutic activity⁶⁹ and senolytics (dasatinib and quercetin)⁶⁸. Moreover, an accumulation of B cells and immunoglobulins can induce senescence in macrophages⁷⁰. Osteopontin, a SASP component, promotes macrophage senescence through both autocrine and paracrine pathways^{71,72}. Deletion of osteopontin in aged macrophages increased MerTK expression, reduced the level of p16^{Ink4a} and restored phagocytic capacity^{71,72}. Finally, an age-related reduction in IL-4, which normally promotes tissue homeostatic macrophages and DNA repair activity, leads to an accumulation of DNA damage and a senescent phenotype of macrophages⁷³. Recombinant IL-4 supplementation reduced macrophage senescence, mitigated DNA damage and extended healthspan in aged mice⁷³. Together, these findings highlight how age-related changes in macrophage function – shaped by both intrinsic and extrinsic signals – can contribute to the propagation of senescence and systemic ageing.

Neutrophils

Neutrophils are short-lived early responders in inflammatory responses and require precise and tightly regulated recruitment to inflamed sites. Interestingly, neutrophils exhibit a distinct phenotype after extended time in the circulation⁷⁴. This is characterized by their upregulation of CXCR4 and an increased pro-inflammatory phenotype⁷⁴. Neutrophils from older individuals also exhibit dysfunctional recruitment and activity when compared to neutrophils from younger individuals⁷⁵. Increased levels of mast cell-derived CXCL1 and endothelial cell-expressed atypical chemokine receptor 1 (ACKR1) impair CXCR2-mediated directional chemotaxis of neutrophils, causing them to re-enter the blood circulation during ageing⁷⁶. A multilayered omics approach analysing bone

marrow-derived neutrophils demonstrated sex-dimorphic regulation on chromatin-related pathways and chromatin architecture⁷⁷. Neutrophils from older individuals also exhibit altered phagocytic capacity and production of neutrophil extracellular traps in a sex-specific manner⁷⁷. These age-associated dysfunctions in neutrophils contribute to remote organ injury, as dysregulated neutrophils disseminate to the lungs and promote vascular leakage during ageing^{76,77}.

Natural killer cells

Natural killer cells exhibit a marked reduction in their cytotoxicity and cytokine-producing and degranulation capacities with age, failing to kill target cells and coordinate the required immune responses⁷⁸. Adoptive transfer experiments suggest that the cytotoxic function of natural killer cells is affected by the age of the host through a cell non-autonomous mechanism⁷⁹. Natural killer cells from older humans also show decreased expression of activating receptors, such as NKp36 and NKp40, indicating that they are less responsive to activating ligands⁸⁰. Telomere attrition also alters natural killer cell activity, as both the cytokine-producing CD56^{bright} natural killer cell and cytotoxic CD56^{dim} natural killer cell populations exhibit shortening of telomeres with ageing⁷⁸. Thus, despite an expansion of the CD56^{dim} natural killer cell population in older individuals, these cells exhibit a reduced cytotoxic capacity that likely limits senescent cell clearance, increasing the senescent cell burden and inflammation^{45,81}.

Type 2 innate lymphoid cells

Type 2 innate lymphoid cells (ILC2s) originate from fetal liver and bone marrow and proliferate in response to IL-33. ILC2s promote homeostasis in non-lymphoid tissues by secreting type 2 cytokines (IL-5 and IL-13) and by regulating other type 2 immune cells. In older individuals, the numbers of ILC2s decline in the lung and white adipose tissue despite increased differentiation of HSCs into the ILC2 lineage with age^{82,83}. The loss of ILC2 numbers is not well understood but is partly due to changes in IL-33 levels, changes in IL-33 receptor expression and differences in ILC2 recruitment capacity. ILC2s also show differential transcription profiles and impaired functionalities marked by reduced type 2 cytokine secretion^{82,83}. Lung ILC2s exhibit decreased IL-5 secretion and perturbations in metabolic pathways that are essential for their function⁸². Elevated levels of IL-12 and IL-18 in older organisms also reduces the number and function of lung ILC2s through unknown mechanisms⁸². Unlike in other tissues, ILC2s accumulate in the brain with age but exhibit reduced activation and lower IL-5 and IL-13 expression⁸⁴. Intracerebroventricular transfer of activated ILC2s or expansion with recombinant IL-5 improved cognitive function and neurogenesis and alleviated neuroinflammation in aged mice⁸⁴. In contrast to ILC2s, the effects on ageing of type 1 and type 3 innate lymphoid cells are largely unexplored.

$\gamma\delta$ T cells

$\gamma\delta$ T cells recognize diverse antigens in an MHC-independent manner and maintain their effector functions by producing IFN γ and/or IL-17. With age, $\gamma\delta$ T cells exhibit decreasing clonality and tissue repair capacities while acquiring cytolytic function profiles across multiple tissues⁸⁵. An age-dependent expansion of $\gamma\delta$ T cells occurs in both secondary lymphoid and peripheral tissues, including spleen, lung, adipose and gut⁸⁵. Adipose $\gamma\delta$ T cells from older individuals are biased towards production of IL-17 but not of IFN γ , and display a tissue-resident memory phenotype⁸⁶. Of note, IL-17 can drive senescence but the contribution of $\gamma\delta$ T cells to secondary senescence is unclear⁸⁷. The age-dependent

accumulation of adipose $\gamma\delta$ T cells is driven by increased proliferation of these cells and reduced *Bcl2*-independent apoptotic signalling⁸⁸. Notably, genetic deficiency of $\gamma\delta$ T cells improves the metabolic function and dampens systemic and local inflammation in aged mice⁸⁶.

Intrinsic immune ageing

In the sections above, we have highlighted the main changes that occur in distinct immune cell populations during ageing. In the following section, we discuss intracellular changes that are observed with age and explore their potential causal roles in driving immune ageing. The 13 hallmarks of ageing (Box 3) emphasize both cell-autonomous and non-cell-autonomous changes with age^{89,90}. We highlight how some of these key hallmarks contribute to immune dysfunction with ageing, focusing on genomic instability, telomere attrition, mitochondrial dysfunction, epigenetic alterations and the loss of proteostasis (Fig. 2).

Genomic instability

Genome integrity is regulated by highly conserved mechanisms that detect and repair DNA damage. Genetic mutations important for DNA repair lead to numerous progeria syndromes, including xeroderma pigmentosum, Cockayne syndrome, Fanconi anaemia, Werner syndrome and Bloom syndrome. For example, mutations in *ERCC1* or its heterodimer partner *XPF*, which encodes a DNA endonuclease involved in multiple types of DNA repair, are linked to xeroderma pigmentosum and Fanconi anaemia. In these human diseases and in mouse models, the reduction in DNA repair activity results in changes in immune function similar to natural ageing. Haematopoietic cell-specific deletion of *Ercc1* in a mouse model led to early onset of immune dysfunction, characterized by increased expression of markers of exhaustion and senescence, along with enhanced secretion of SASP factors, mirroring the changes that are observed during natural ageing⁴. Notably, most splenic immune cells in this mouse model exhibit increased expression of the cell-cycle arrest proteins *p16^{Ink4a}* (also known as *Cdkn2a*) and *p21^{Cip1}* (also known as *Cdkn1a*) and higher levels of SASP factors; however, B cells only exhibit increases in *p16^{Ink4a}* and *p21^{Cip1}* without the parallel increase in SASP expression⁴. Peripheral tissues in these animals, including the brain, kidney, liver, adipose tissue and spleen, also show increased signs of senescence and overall tissue damage, and this is accompanied by reduced lifespan and heightened systemic inflammation in mice⁴. Furthermore, adoptive transfer of either *Ercc1*-deficient splenic cells or splenic cells from older mice into young mice induced widespread senescence, inflammation and tissue damage in the young recipient, which is consistent with immune cell-driven paracrine senescence inducing pathophysiology with ageing. By contrast, transfer of wild-type immune cells from a young mouse into an aged mouse alleviated these pathological features, demonstrating the potential for immune rejuvenation to improve age-related pathologies⁴. Accumulating DNA damage also leads to an accumulation of regulatory T (T_{reg}) cells and the activation of naive T cells, which resembles changes seen in T cell populations in naturally aged mice⁹¹. Antigen-naive, but semi-differentiated virtual memory T cells exhibit higher levels of DNA damage and proliferative defects as compared to central memory T cells during ageing⁵⁴. However, the proliferative defects seen in naive CD8⁺ T cells from old mice cannot be restored even when they are transferred to a young host, suggesting that DNA damage may be an irreversible characteristic of old T cells⁵⁴.

Telomere attrition

Telomeres maintain genome stability and their loss is linked to cellular senescence in multiple cell types⁹². Age-dependent telomere shortening

Box 3 | The main hallmarks of ageing

The 13 hallmarks of ageing^{89,90} are considered a foundational principle in ageing biology, and they offer guidelines for understanding age-related dysfunction in immune cells. These hallmarks are interdependent factors, and experimental accentuation or attenuation of one hallmark usually affects other processes. The 13 hallmarks are: genomic instability, telomere attrition, epigenetic alteration, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, extracellular matrix (ECM) changes, stem cell exhaustion, altered intercellular communication, chronic inflammation and dysbiosis.

Of note, ECM remodelling has recently been introduced as a hallmark of ageing⁹⁰, and its reciprocal interactions with the immune system are an area of growing interest¹⁸⁷. The ECM is in direct contact with immune cells and has a critical role in regulating their localization, activation and functions, through both biochemical and biophysical cues¹⁸⁷. With ageing, ECM undergoes significant structural and compositional changes, altering its crosstalk with immune cells¹⁸⁸. These age-related changes in ECM-immune interaction can converge to impact tissue homeostasis and disease progression, particularly in the tumour microenvironment¹⁸⁸. Considering the widespread ECM remodelling that is seen with age, further investigations on reciprocal links between ECM and the immune system in the ageing context are required.

also occurs across multiple immune cell types, including most T cell subsets, B cells, macrophages and natural killer cells^{78,93–95}. In older individuals, telomere length is associated with immune robustness, affecting B cell and CD8⁺ T cell responses to influenza virus infection⁹³. B cells and CD8⁺ T cells with longer telomeres show enhanced antibody production and greater population expansion following vaccination⁹³. Moreover, an increased influenza virus-specific CD8⁺ T cell count post-vaccination is predominantly observed in individuals with longer telomeres⁹³. A decline in telomerase activity, which is essential for telomere maintenance, limits the ability of aged T cells to proliferate following antigen stimulation⁹⁶. Age-related telomere shortening in macrophages is also associated with reduced proliferative capacity and enhanced oxidative stress, similar to what is seen in telomerase-deficient macrophages⁹⁴. These mutant macrophages secrete elevated inflammatory cytokines due to aberrant NLRP3 inflammasome activation and mitochondrial dysfunction, resulting in a cytokine storm, severe lung inflammation and higher mortality upon respiratory infection⁹⁴. Interestingly, antigen presenting cells can transfer telomeres to T cells, primarily naive and central memory T cells, through direct contact⁹⁶. This mechanism supports their proliferation needs by enabling telomere elongation independently of telomerase, which may be impaired during ageing⁹⁶.

Mitochondrial dysfunction

Mitochondria are crucial organelles that orchestrate intracellular and extracellular energy demands and their dysfunction has been linked to systemic ageing and age-associated diseases^{97,98}. Experiments involving deletion of the mitochondrial transcription factor TFAM, which maintains mitochondrial integrity by stabilizing mtDNA, in specific immune cell subsets have highlighted an important role for functional mitochondria in immune ageing^{6,7,99}. CD4⁺ T cell-specific

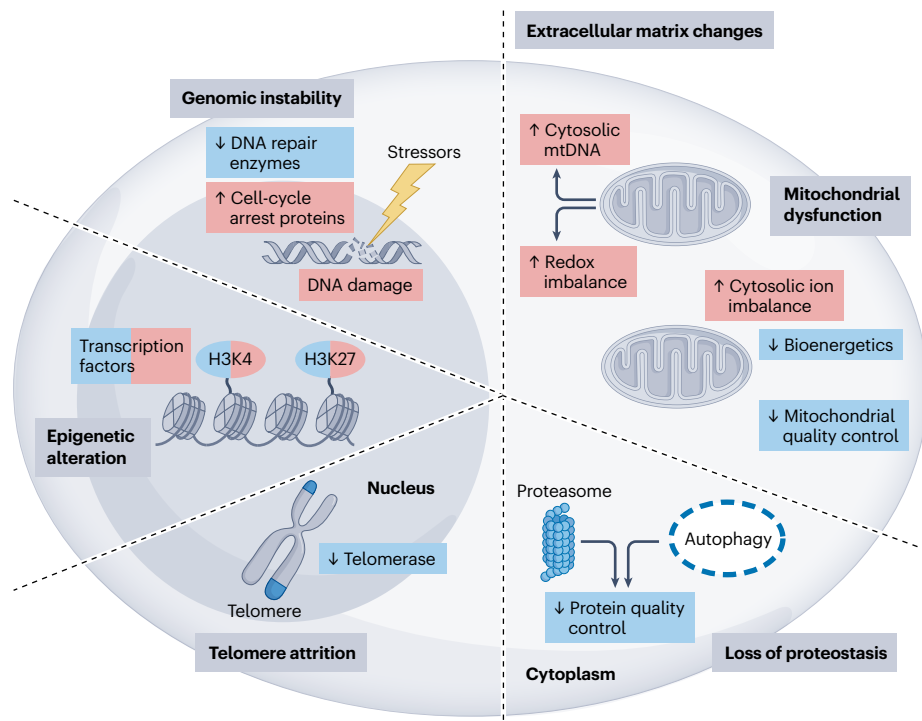


Fig. 2 | Key features of cell-intrinsic ageing. Cell-autonomous mechanisms of ageing include increased genomic instability, extracellular matrix changes (Box 3), mitochondrial dysfunction, loss of proteostasis, telomere attrition and epigenetic alterations. Of note, these features are highly interdependent (Box 3). Genomic instability arises from accumulated DNA damage due to elevated cellular stress, increased expression of cell-cycle arrest proteins, and reduced activity of repair enzymes. Mitochondrial dysfunction is characterized by compromised bioenergetics, disrupted cytosolic ion homeostasis, increased redox imbalance and mitochondrial DNA (mtDNA) release into the cytosol. Proteostasis alters owing to impaired autophagy and proteasome activities,

leading to accumulation of misfolded or damaged proteins. Telomere attrition results from reduced telomerase capacity and may also involve impaired intercellular telomere transfer. Epigenetic alterations include shifts in histone modification marks (for example, H3K27me3 and H3K4me3) and DNA methylation, affecting chromatin accessibility and transcriptional activities. These features are adapted from the hallmarks of ageing. Processes and factors that are increased with ageing are labelled in red, whereas decreased or dysfunctional processes are labelled in blue. For discussion of their specific relevance to immune cell types and immune ageing, refer to the main text.

Tfam deletion leads to increased expression of IFN γ and TNF, increased age-associated multimorbidity, and shorter lifespan⁶. B cell-specific deletion of *Tfam* promotes the accumulation of memory B cells and age-associated B cells while impairing germinal centre reactions, replicating age-associated dysfunction of B cells⁷. Interestingly, myeloid cell-specific deletion of *Tfam* suggested that the role of mitochondria in regulating macrophage phenotypes varies depending on the tissue type⁹⁹. While deletion of *Tfam* reduced inflammatory phenotypes in adipose tissue macrophages, it promoted the death of alveolar macrophages⁹⁹.

Mitochondria also shape inflammatory responses in macrophages by regulating cytosolic ion homeostasis, particularly Ca²⁺ uptake. Expression of the mitochondrial Ca²⁺ uniporter is reduced in macrophages from older mice and older humans. Similarly, mitochondrial Ca²⁺ uniporter-deficient macrophages or aged macrophages have amplified cytosolic Ca²⁺ oscillations, show increased activation of NF- κ B and the NLRP3 inflammasome, and display enhanced cytokine production¹⁰⁰. Interestingly, cytosolic mtDNA released by aged, dysfunctional mitochondria due to minority mitochondrial outer membrane permeabilization activates the cGAS–STING pathway to promote senescence and inflammation during ageing¹⁰¹. Pharmacological

inhibition of BAX to inhibit minority mitochondrial outer membrane permeabilization formation reduced the SASP in microglia and oligodendrocytes, alleviated inflammation, and improved healthspan in aged mice¹⁰¹.

Epigenetic alterations

Altered chromatin dynamics and epigenetic modifications are seen in all immune cell populations from older individuals¹⁰². These changes, especially in peripheral blood mononuclear cells, have been used to develop epigenetic clocks to determine the biological age of an organism^{103,104}. Monocytes, CD56⁺ natural killer cells and CD8⁺ memory T cells all show increased chromatin accessibility in genes associated with inflammation, while naive T cells show an overall loss of chromatin accessibility in such genes¹⁰⁵. Although both male and female individuals exhibit similar age-associated alterations in chromatin accessibility, these changes are more pronounced in male individuals¹⁰⁵. For example, monocytes from both male and female older humans show increased chromatin accessibility to inflammation-related genes, such as *IL18*, *IL1B*, and *S100A8* and *S100A9*, but a greater overall increase is seen in male monocytes¹⁰⁵. Monocytes also exhibit increased H3K4me1-enriched hypomethylation regions in older male individuals¹⁰⁶.

Ageing also affects B cell epigenetics in a sex-specific manner. B cell-specific loci and genes show modest differences in female individuals but significant closing of peaks and inactivation of genes occurs in male individuals, which may contribute to sex differences in autoimmunity and humoral responses¹⁰⁵. Multi-omics profiling of neutrophils also demonstrates age-related and sex-dimorphic chromatin regulation⁷⁷. A mouse model that replicates age-associated loss of Y-chromosome (Box 4) further highlights sex-specific consequences of ageing¹⁰⁷. Targeted Y-chromosome loss within haematopoietic cells promotes cardiac fibrosis and heart failure-related mortality in male mice¹⁰⁷. Furthermore, the increase in inflammatory macrophages and cardiac fibrosis was regulated by histone methylation, a UTY-mediated epigenetic modification¹⁰⁸ (see Box 4 for additional information on sex dimorphisms). Together, these data define differences in the sex-specific epigenome and provide some context for a causal role in promoting age-related diseases.

Differential transcription factor activities also contribute to altered chromatin accessibility and favour elevated immune responses

during ageing. In naive T cells, imbalanced activation of the transcription factors HELIOS and STAT5 skews their differentiation towards pro-inflammatory effector T cells (discussed above in the T cell section)⁴³. The AP-1 transcription factor complex, which is composed of Jun and Fos members, increases in splenic and peripheral T cells with age¹⁰⁹. In aged T cells, AP-1 has elevated binding activity and targets multiple inflammatory genes, such as *Il6*, that are more accessible and actively transcribed. AP-1 complex activation also affects the transcription of inflammatory genes and chromatin accessibility in B cells, T cells, natural killer cells and macrophages during ageing, supporting an inflammatory phenotype¹⁰⁹. Moreover, the SMAD2–SMAD3–SMAD4 transcription factor complex regulates chromatin accessibility in aged macrophages, skewing their phenotypes towards a pro-inflammatory state, via amplified GDF3 signalling in old organisms¹¹⁰. Finally, reduced phagocytosis, migration and chemotaxis of monocyte-derived macrophages from older donors (>50 years old) is linked to decreased transcription activity of MYC and USF1 (ref. 111). Altogether, these findings highlight the need for future studies to dissect how epigenetic

Box 4 | Sex dimorphism, autoimmunity and immune ageing

Numerous studies have described the sex-dimorphic features of the immune system that contribute to sex-specific responses to infection, autoimmunity and cancer^{189–191}. Female individuals, for example, generally have a higher life expectancy and lower infection rates than male individuals¹⁸⁹. By contrast, male individuals are less susceptible to autoimmune diseases but have a higher risk of developing cancer¹⁸⁹. As such, immune ageing draws multiple parallels with the development of autoimmunity¹⁹².

Sex disparities are driven by multiple factors, including differences in sex chromosomes and sex hormones. Models using surgical or genetic gonadectomy, as well as sex chromosome manipulations, have been instrumental in dissecting the roles of these factors in immunity and disease susceptibility — though many aspects remain to be explored. For a more comprehensive discussion on sex dimorphism in immunity, we refer readers to the following publications^{189–191}.

Autoimmunity

Autoimmunity is characterized by the loss of immune tolerance, leading to immune responses against self-antigens. Immune ageing is a leading risk factor for the development of autoimmune diseases¹⁹². Age-associated autoimmunity is primarily driven by self-reactive memory T cells and B cells, and is further amplified by chronic, low-grade inflammation. As noted above, sex dimorphism has a crucial role in autoimmune susceptibility, with female individuals exhibiting a higher prevalence of many autoimmune conditions¹⁸⁹. For detailed discussions on autoimmunity and its relation to sex dimorphism, we refer readers to these studies^{190,192,193}.

Sex chromosomes

X-chromosomes and Y-chromosomes are primarily recognized for their ability to confer biological sex; however, they contain numerous immune-related genes. X-chromosome inactivation silences one X-chromosome and is required to balance gene expression between XX female individuals and XY male individuals. Recent reports have highlighted the importance of escape from X-chromosome inactivation that promotes the overexpression of

specific immune-related genes^{60,194,195}. The literature also indicates that loss of the Y-chromosome within haematopoietic cells promotes cardiac fibrosis and heart failure-related mortality in men¹⁰⁷. In mouse models, this results in an increase in pro-inflammatory macrophages that cause cardiac fibrosis, with epigenetic modifications regulated by the *UTY* gene driving fibrotic gene expression¹⁰⁸. Immune cell loss of the Y-chromosome is associated with kidney injury and a higher level of cellular senescence¹⁹⁶. In male mice reconstituted with bone marrow lacking the Y-chromosome, there was increased senescent cell accumulation with age and in models of kidney injury¹⁹⁶. These studies are consistent with the idea that sex chromosomes regulate immune activation and contribute to tissue functional decline, supporting sex-dimorphic age dysfunction.

Reproductive organs and sex hormones

In the ovary, immune cells have a central role in regulating key reproductive functions; however, with age, the ovary exhibits inflammation and fibrosis, along with a reduction in adaptive immune cells and altered function of innate immune cells¹⁹⁷. Interestingly, metformin treatment increases specific macrophage subsets, chemokine-dependent crosstalk with fibroblasts and reduces senescence-associated secretory phenotype-associated inflammation¹⁹⁷. Similarly, the ageing prostate exhibits an inflammatory microenvironment that contributes to benign prostatic hyperplasia, a shift in immune composition, and increased inflammatory cytokines such as IL-6, which feeds into an androgen receptor-dependent hyperplasia¹⁹⁸. Gonadectomy has sex-specific effects on lifespan; it extends lifespan in female mice but reduces it in male mice¹⁹⁹. Gonadectomy is also linked to systemic anti-inflammatory effects of sex hormones on immune regulation in remote non-reproductive organs¹⁸⁹. For example, ovariectomy elevated inflammation in the liver and adipose tissue¹⁹⁹, and the immunomodulatory effects of sex hormones are increasingly recognized in diverse organ systems. For a comprehensive overview of sex hormone–immune interactions in ageing, see ref. 189.

Review article

and transcriptional regulators drive immune cell ageing, which may uncover new strategies for preventing age-related immune dysfunction.

Loss of proteostasis

Proteostasis, which is important for protein quality control, becomes dysregulated in immune cells from older individuals. For example, aged CD4⁺ T cells exhibit defective proteasome activation that normally regulates TCR activation¹¹². T cell-specific deletion of the proteasome subunit *Rpn13* leads to reduced numbers of naive CD4⁺ T cells and increased numbers of PDI⁺ memory T cells, similarly to what is seen in the overall T cell compartment with age. Autophagy is another crucial mechanism for maintaining proteostasis, and its regulation declines with age in multiple immune cell types, including B cells and T cells¹¹³. In B cells, decreased levels of spermidine (an endogenous polyamine metabolite that modifies the translation factor eIF5A) reduces autophagy by blocking the translation of the transcription factor TFEB¹¹⁴. Spermidine supplementation restores these pathways and leads to improved antibody production capabilities¹¹⁴. The roles of spermidine in regulating autophagy and function are also seen in T cells from older individuals¹¹⁵. Finally, a subset of aged HSCs with increased autophagy retains their regenerative capabilities as a result of metabolic adaptation to SOCS3-mediated inhibition of glycolysis¹¹⁶. Transient autophagy induction through short-term fasting and refeeding increases regenerative potential and normalizes glycolysis in aged HSCs¹¹⁶.

Effect of immune ageing on organs

The ageing immune system is recognized as a key factor driving multi-organ dysfunction with age. Here, we discuss the major features identified in aged organs that stem from immune ageing, including tissue-specific dysfunctional interaction between immune cells, altered microenvironment architecture, increased fibrosis and loss

of stromal cell identity, macrophage activation, and accumulation of lymphocytes^{12,56,57,59,70,117–119} (Fig. 3 and Table 1). Whether immune-driven tissue dysfunction can be effectively reversed remains an open question, underscoring the need to develop strategies that intervene or reverse these changes to mitigate systemic ageing.

Spleen

The spleen is a critical lymphoid organ for red blood cell clearance, antigen presentation, T cell–B cell interactions, and B cell maturation. There is an increase in the frequency of splenomegaly in older individuals, which is characterized by an altered immune cell composition and impaired clearance of red blood cells. Red blood cells accumulate damage over time and show molecular changes consistent with cellular senescence¹²⁰. Platelets are more likely to form complexes with senescent red blood cells, suggesting that dysfunctional aged platelets or the numerical decline in platelets may contribute to risk for thrombosis and immune activation in older individuals¹²¹. The quality of splenic germinal centres, formed to generate memory B cells and plasma cells that provide protection against infection, decline with age. Splenic T follicular regulatory cells increase in number and are more likely to express FOXP3 and IL-10, which suppress B cell antibody production¹²². In addition, type 2 classical dendritic cells, which are critical for priming follicular helper T cells, show reduced expression of CD80 and CD86 as well as reduced *Irf1*, which impairs the follicular helper T cell-priming capacity of type 2 classical dendritic cells post-vaccination¹²³. The aged splenic microenvironment also promotes differentiation towards extrafollicular antibody producing B cells but not memory B cells¹²⁴.

Adipose tissue

White adipose tissue (WAT) is a major endocrine organ responsible for the storage of lipid. With age, WAT fails to mobilize energy in response

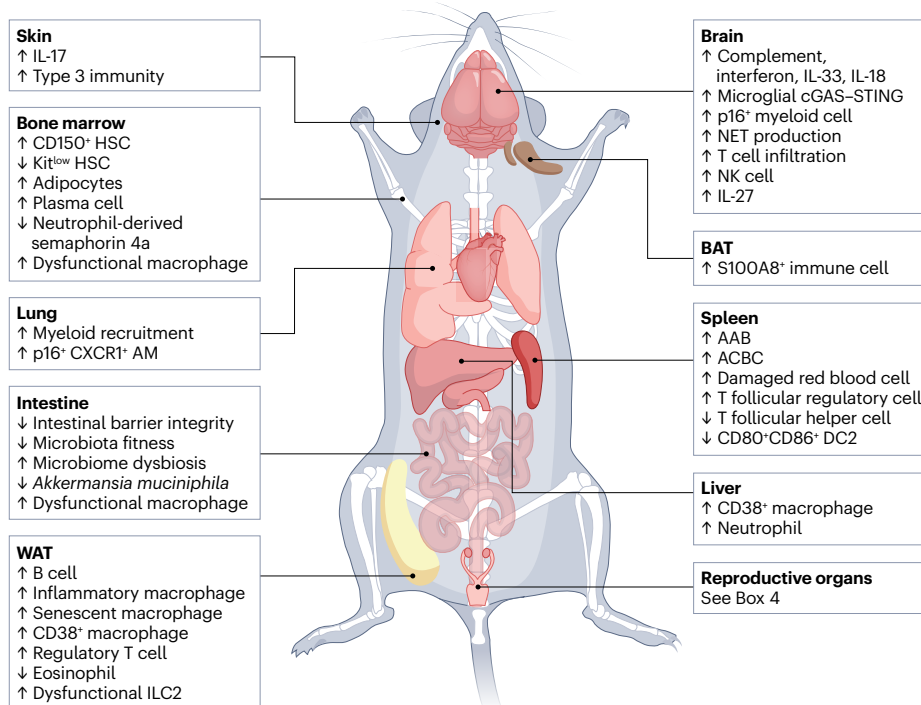


Fig. 3 | Impact of immune ageing on organ function in mice.

The consequences of immune ageing on organ dysfunction across lymphoid and non-lymphoid tissues are described here. In lymphoid tissues, ageing results in thymic involution, reduced naive T cell output, restricted receptor repertoire, and disrupted splenic and lymph node architectures, with a particular focus here on splenic immune composition changes. In non-lymphoid tissues, ageing promotes senescence, inflammation and fibrosis, driven by alterations in immune composition and associated factors such as cytokines. Age-related changes in reproductive organs are highlighted in Box 4. See Table 1 also for more details. AAB, age-associated B cell; ACBC, age-associated clonal B cell; AM, alveolar macrophage; BAT, brown adipose tissue; DC2, type 2 dendritic cell; HSC, haematopoietic stem cell; ILC2, type 2 innate lymphoid cell; NET, neutrophil extracellular trap; NK, natural killer; WAT, white adipose tissue.

Table 1 | Age-associated immune changes and impact on different tissues

| Tissue | Age-associated changes in immune cells | Mechanisms involved | Functional consequences | Refs. |
|----------------|--|---|--|---------------------|
| Bone marrow | ↑ CD150 ⁺ HSCs | ↑ Epigenetic alterations | Increased myelopoiesis and compromised immunity | 17,18 |
| | ↓ Kit ^{low} HSCs | – | Decreased lymphopoiesis and compromised adaptive immunity | 23 |
| | ↑ CHIP | ↑ TET2, DNMT3A-driven selective expansion of mutant progeny cells | Increased myelopoiesis (via DNMT3A) | 25–27 |
| | ↑ BM adipocytes | ↑ Proximity between adipocytes and HSCs | Decreased HSC number and self-renewal capacity, and increased inflammatory cytokines | 33 |
| | ↑ BM plasma cells | ↑ IL-1β and TNF | Increased myelopoiesis and BM stromal cell activation | 35 |
| | Altered BM neutrophil function | ↑ Semaphorin 4a | Increased myelopoiesis through AP-1 family | 34 |
| | ↑ Dysfunctional macrophages | ↑ IL-1β, caspase 1 ↓ Efferocytosis | Increased senescent neutrophils supporting platelet-biased HSC expansion | 186 |
| Spleen | ↑ Dysfunctional platelets | ↑ Complex formation with damaged red blood cells | Increased risk for thrombosis and immune activation | 121 |
| | ↑ T _{FR} cells, ↓ T _{FH} cells | ↑ PD1, ↓ antigen-specific response | Decreased GC formation and B cell maturation | 122 |
| | ↓ cDC2 | Decreased GC formation and B cell maturation | Decreased GC formation and B cell maturation | 123 |
| | ↑ ACBCs | ↑ High clonality | Not reported | 44 |
| Adipose tissue | ↑ Inflammatory macrophages | ↑ IL-1β, caspase 1, SMAD2/SMAD3, CD38, osteopontin | Increased inflammation and metabolic dysfunction | 71,110,118, 129,130 |
| | ↑ SPARC | ↑ TLR4-mediated macrophage activation | Increased inflammation | 67 |
| | ↑ B cell | ↑ Immunoglobulin ↑ Macrophage-derived TGFβ1 | Increased fibrosis and metabolic dysfunction | 70 |
| | ↑ Eosinophils, T _{reg} cells | ↑ IL-10 | Compensate for increased inflammation | 132,133 |
| | ↑ γδ T cells | ↑ Proliferation | Increased inflammation | 86,88 |
| | ↑ S100A8 ⁺ cells, dysfunctional type 2 ILCs | – | Decreased thermogenic capacity | 134 |
| Liver | ↑ CCR2 ⁺ macrophages | ↑ Infiltration | Increased inflammation | 135 |
| | ↑ CD38 ⁺ macrophages | ↑ Senescent cells | NAD ⁺ decline and mitochondrial dysfunction | 129–131 |
| | ↑ Neutrophils | ↑ ROS | Increased senescence | 136 |
| Skin | Activation of T _H 17 cells, γδ T cells and ILCs | ↑ IL-17 | Increased type 3 immunity, epidermal inflammation and dermal thickness | 138 |
| Brain | ↑ Inflammatory microglia | ↑ cGAS–STING activation | Increased microgliosis and neurodegeneration | 141 |
| | ↑ p16 ⁺ myeloid cells | – | Activation and infiltration of immune cells, cognitive decline | 143 |
| | ↑ Myeloid infiltration | ↑ CHIP | Protection from Alzheimer disease | 30,31 |
| | ↑ Dysfunctional neutrophils | ↑ NET production | Decreased revascularization | 142 |
| | ↑ T cell infiltration | ↑ Clonal expansion and IFNγ | Decreased neural stem cell proliferation | 147 |
| | ↑ T _{reg} cells | ↓ Oligodendrocyte differentiation and myelination | Decreased regenerative capacity | 148 |
| | ↑ NK cells | ↑ IL-27R mediated cytotoxicity | Increased neuroinflammation and cognitive decline | 149 |
| Lung | ↑ Monocyte-derived alveolar macrophages | ↑ Myelopoiesis, ↑ IL-1α, fibrotic phenotype | Increased inflammation and fibrosis | 15,149,150 |
| | ↓ Homeostatic macrophages | ↓ IL-10 | Increased inflammation and fibrosis | 151 |
| | ↑ p16 ⁺ CXCR1 ⁺ alveolar macrophages | Not reported | Reduced T cell cytotoxicity, increased tumorigenesis (lung tumour model) | 153 |
| Gut | ↑ Macrophage dysfunction | ↑ IL-6, TNF | Increased microbial dysbiosis | 74,167 |

ACBC, age-associated clonal B cell; BM, bone marrow; cDC2, type 2 classical dendritic cell; CHIP, clonal haematopoiesis of indeterminate potential; DNMT3A, DNA methyltransferase 3A; GC, germinal centre; HSCs, haematopoietic stem cells; ILCs, innate lymphoid cells; NET, neutrophil extracellular trap; NK, natural killer; ROS, reactive oxygen species; SPARC, secreted protein acidic and rich in cysteine; T_{FH} cell, T follicular helper cell; T_{FR} cell, T follicular regulatory cell; T_H17 cell, T helper 17 cell; TLR4, Toll-like receptor 4; TNF, tumour necrosis factor; T_{reg} cell, regulatory T cell.

to cues such as fasting, infection and cold exposure. The reduced functionality of WAT is driven by an accumulation of macrophages, B cells and $\gamma\delta$ T cells that adopt inflammatory phenotypes during ageing^{59,86,118}. Inflammatory pathways, including the NLRP3 inflammasome, IL-1 β and TNF, that support local changes in chemokines, are largely responsible for leukocyte accumulation in WAT¹²⁵. The production of IL-1 β supports B cell proliferation and their accumulation in WAT^{59,126,127}, and the age-related increase in B cell-derived immunoglobulin within WAT and other tissues promotes macrophage senescence and activation^{70,128}. In turn, activated macrophages produce the pro-fibrotic cytokine TGF β 1 and this promotes fibrosis in WAT from older mice¹²⁸. Interventions targeting B cells or immunoglobulin reverse fibrosis and metabolic dysfunction with age, implicating the macrophage–B cell interaction as a promising therapeutic target¹²⁸.

Macrophages from the WAT of old mice show increased expression of CD38, a critical enzyme that metabolizes NAD⁺, which is instrumental in cellular functions such as chromatin remodelling and DNA repair^{129,130}. p16^{Ink4a+} senescent cells further exacerbate this process by promoting the proliferation of CD38⁺ inflammatory macrophages^{129,130}. The removal of p16^{Ink4a+} cells or a lifelong CD38 deficiency results in improved metabolic functions as indicated by improved mitochondrial function and better glucose sensitivity, extending healthspan^{129,131}.

There is evidence of immunosuppressive mechanisms in WAT that may reduce inflammation. T_{reg} cells are critical immunosuppressive cells that produce IL-10 and sensitize WAT to immunological cues. Counterintuitively, levels of T_{reg} cells and T_{reg} cell-derived IL-10 increase with age in WAT, suggesting a compensatory but insufficient attempt to counteract the increased inflammation that occurs in ageing WAT¹³². Additionally, despite higher WAT levels of CCL11, which recruits eosinophils, these immunoregulatory cells also decrease with age¹³³. The adoptive transfer of young eosinophils into an aged host reverses the physical decline in an IL-4-dependent manner¹³³.

Compromised thermogenic potential of adipose tissue depots is also driven by ageing immune cells. Inflammatory S100A8⁺ immune cells selectively accumulate in brown adipose tissue with age¹³⁴. S100A8⁺ immune cells, mainly composed of neutrophils and T cells, exhibit senescent phenotypes and form neuroimmune–adipose interfaces that inhibit sympathetic innervation, reducing the signalling pathways to activate thermogenesis¹³⁴. Transfer of S100A8⁺ cells into young mice is sufficient to induce thermogenic failure, underscoring their detrimental role in ageing¹³⁴.

Liver

The aged liver exhibits an accumulation of immune cells and senescent cells, increasing ectopic fat accumulation and inflammation. Infiltrating CCR2⁺ monocyte-derived macrophages promote hepatocyte inflammation, which can be prevented by deleting *Ccr2* to reduce their infiltration¹³⁵. CD38⁺ macrophages also increase in the liver in a senescent cell-dependent manner, contributing to NAD⁺ decline and subsequent mitochondrial dysfunction with age^{129–131}. Neutrophils are recruited by the increase in the number of senescent non-immune cells, further propagating senescence to neighbouring cells in a ROS-dependent manner¹³⁶. Hepatocytes, the predominant cell type in liver, undergo significant age-related changes, including increased iron-dependent cell death and antigen binding, which require multifaceted immune regulation¹³⁷. However, the roles of other immune cells, such as B cells, T cells and other innate-like cells, in liver ageing and associated pathologies are unclear.

Skin

The skin is especially susceptible to genotoxic and cellular stress during ageing. Skin ageing is accompanied by an increase in levels of IL-17, which is produced by CD4⁺ T cells, $\gamma\delta$ T cells and innate lymphoid cells. IL-17 promotes epidermal inflammation, including NF- κ B activation, the production of inflammatory cytokines and altered dermal thickness¹³⁸. Neutralization of IL-17 reduced inflammation and improved hair follicle growth in mouse models¹³⁸. These results are consistent with the increased IL-17 signalling signatures identified during injury of aged animals¹³⁹. Intriguingly, this analysis in the skin identified a crosstalk between senescent cells and T cells that promoted IL-17-mediated type 3 immunity, which typically drives epithelial antimicrobial responses¹³⁹. Neutralizing IL-17 prevented type 3 immune activation, improved wound healing and promoted muscle repair¹³⁹.

Brain

Molecular signatures of the ageing brain have demonstrated that oligodendrocytes, microglia, endothelial cells and astrocytes all show distinct age-related transcriptional profiles, including an upregulation of complement, cytokines (IL-33 and IL-18) and interferons¹⁴⁰. In aged microglia, increased cytosolic mtDNA activates the cGAS–STING pathway¹⁴¹. Blocking this pathway mitigates microgliosis, reduces the interferon-stimulated gene signatures and alleviates neurodegeneration¹⁴¹. Microglia from aged female mice produce more complement and exhibit amplified AKT–mTOR–HIF1 α -mediated signalling with a shift towards glycolysis, which may contribute to sex differences in neurodegeneration¹⁴². The p16^{Ink4a+} myeloid cells that increase in the ageing mouse brain exhibit senescent-like and disease-associated activation signatures¹⁴³. Furthermore, p16^{Ink4a+} senescent cell clearance reduces activated resident and infiltrating immune cells and preserves cognitive function¹⁴³. By contrast, neutrophil extracellular trap production and the downstream inflammation impairs revascularization and contribute to age-related cognitive decline^{144,145}. Moreover, increased oxidative stress, phagocytosis and procoagulant features of neutrophils from older individuals are linked to worse outcomes following stroke¹⁴⁶.

There is also T cell infiltration into the aged brain, including CD8⁺ T cells with an exhausted and IFN γ signature, as well as of T_{reg} cells with impaired regenerative capacity¹⁴⁷. T_{reg} cells in the aged brain exhibit diminished capacity to promote MCAMI-mediated and ITGA2-mediated oligodendrocyte differentiation and myelination that can be rescued by a young tissue environment¹⁴⁸. Natural killer cells in the brain also show distinct differences with age¹⁴⁹. They are increased in numbers and display a distinctive transcriptional profile with increased activation and cytotoxicity with age¹⁴⁹. Neuroblast-expressed IL-27 promotes the local cytotoxicity in natural killer cells through IL-27R, increasing neuroinflammation, and highlighting the impact of a tissue niche on natural killer cell function during ageing¹⁴⁹.

Lung

The balance of tissue-resident and recruited immune cells maintain lung respiratory capacity and support healing upon infection or injury. Recruited monocyte-derived, but not tissue-resident, alveolar macrophages, contribute to lung fibrosis and persist even after resolution¹⁵⁰. This persistence is more prominent in older organisms¹⁵⁰, regulated by myeloid skewing in HSCs with age^{15,151}. Reduced IL-10, a critical immunosuppressive cytokine, in lung T_{reg} cells from old mice limits monocyte-derived alveolar macrophages to obtain homeostatic phenotypes, instead promoting fibrotic and inflammatory phenotypes¹⁵¹. Bone marrow transplantation from old donors to young recipients suggests

that cell-intrinsic features are key determinants of these lung pathologies¹⁵¹. However, adoptive transfer and parabiosis revealed that the aged microenvironment is also responsible for the dysfunction and hyper-inflammatory actions of alveolar macrophages¹⁵². Moreover, p16^{Ink4a+} CXCR1⁺ alveolar macrophages increase with ageing¹⁵³. Considering that removal of p16^{Ink4a+} cells, including macrophages, attenuates tumorigenesis and restores a cytotoxic T cell population in a lung tumour model, the reciprocal interaction between p16^{Ink4a+} cells, macrophages and cytotoxic T cells may promote lung dysfunction in the elderly¹⁵³.

Potential for immune rejuvenation

Given the contribution of immune ageing on systemic ageing, improving immune cell function with age should have profound positive effects on reducing multimorbidity, improving resilience and extending healthspan. Here, we discuss several types of interventions that have the potential to improve age-related immune function. These include dietary interventions, microbiome therapy, immunotherapy, senotherapeutics and even partial reprogramming (Fig. 4).

Diet interventions

Dietary interventions range from calorie restriction to time compressed eating to targeted nutrient modulation such as a ketogenic diet. Calorie restriction increases lifespan and has positive effects on immune function, alleviating inflammageing, by reducing interferon-related and pattern-recognition receptor-related gene expression, but without reversing age-related chromatin changes¹⁵⁴. Strikingly, the age-associated decline seen in B cell receptor repertoire diversity in mice was reversed by 40% by caloric restriction, even when initiated at mid-life, whereas no changes in B cell somatic hypermutation or CDR3 length and variability were observed regardless of age or diet¹⁵⁵. Both short-term and long-term 30% caloric restriction also normalize HSC subsets in aged mice¹⁵⁶. Long-term caloric restriction reversed mitochondrial dysfunction and reduced DNA damage-mediated signalling, whereas short-term caloric restriction improved haematopoietic reconstitution in aged animals following the transfer of HSCs¹⁵⁶. In addition, it is noteworthy that exercise elicits an overlapping metabolic effect with those of caloric restriction. Even a 6-week exercise programme in humans resulted in a minor redistribution of naive and memory T cells and reduced IL-10 production from T_{reg} cells¹⁵⁷. An increase in naive T cells and immature natural killer cells (in percentages) predicted longer lifespan, whereas increased effector T cells were linked with a shorter lifespan¹⁵⁸. These correlations became more pronounced with dietary restrictions, suggesting that reconstitution of a youthful immune cell repertoire may underlie the benefits of caloric restriction¹⁵⁸.

The effect of dietary interventions on immune function was also examined in the CALERIE study, a phase II, randomized controlled trial of a 25% caloric restriction diet¹⁵⁹. Two years of moderate caloric restriction significantly reduced multiple cardiometabolic risk factors but also reduced expression of SPARC, an adipocyte-secreted extracellular matrix protein linked to healthspan and lifespan in mice⁶⁷. Caloric restriction also improved thymopoiesis and correlated with better lipid mobilization as well as with improved mitochondrial bioenergetics and anti-inflammatory responses in adipose tissue¹⁶⁰. In addition, expression of platelet activating factor acetylhydrolase (PLA2G7) was reduced in the calorie-restricted individuals, consistent with the observation that deletion of *Pla2g7* in mice decreased thymic lipofattyrophy, protected against age-related inflammation and improved metabolic health¹⁶⁰.

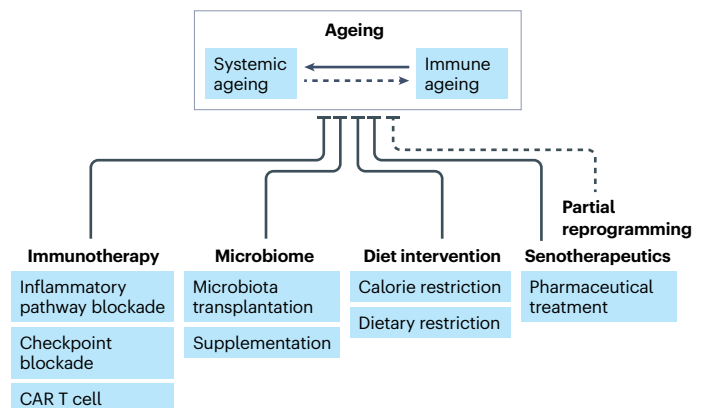


Fig. 4 | Therapeutics that support immune rejuvenation. Systemic ageing is closely linked with immune ageing, creating a self-reinforcing cycle that accelerates functional decline across tissues. Targeting the link between systemic ageing and immune ageing therefore represents a promising approach to alleviate ageing-related pathologies. Several therapeutic routes show promise for the inhibition of this vicious cycle between systemic ageing and immune ageing. These include immunotherapy (inflammatory pathway blockade and checkpoint blockade), microbiome treatment (microbiota transplantation and supplementation), diet intervention (calorie restriction and dietary restriction), senotherapeutics and partial reprogramming of cells. In the schematic, solid lines indicate experimentally validated interactions linking these interventions to improve immune or systemic function, whereas dotted lines represent hypothesized or less well-established connections requiring further studies. CAR, chimeric antigen receptor.

In addition, a ketogenic diet, in which energy reliance is shifted from carbohydrates to fatty acids, reduced NLRP3 inflammasome activation and cytokine production during acute inflammation in mouse models of gout and in influenza virus or SARS-CoV-2 infections^{161–164}. A ketogenic diet also reduced mid-life mortality and improved memory in ageing mice¹⁶⁵.

Microbiome

The gut microbiome undergoes substantial changes with age, including a decline in bacterial diversity, as well as loss of intestinal barrier integrity¹⁶⁶. There is a strong association between gut microbiome composition, the peripheral accumulation of terminally differentiated, senescent and exhausted T cells, and the compensatory expansion of T_{reg} cells in older adults¹⁶⁶. Age-associated microbiome dysbiosis and intestinal permeability also led to increased systemic inflammation, driven in part by higher levels of circulating bacterial products and impaired macrophage function¹⁶⁷. Conversely, germ-free mice show extended lifespan, reduced circulating inflammatory cytokine levels (IL-6 and TNF), improved macrophage-mediated bacterial clearance and a decrease in aged neutrophils in the circulation^{74,167}. Targeting circulating TNF with neutralizing antibody in old mice alleviated microbial dysbiosis, supporting a bidirectional link between age-associated inflammation and microbiome composition¹⁶⁷.

Transferring healthy gut microbiota into infected older adults improved intestinal barrier integrity¹⁶⁶. In addition, aged germ-free mice were protected from increased intestinal permeability and thymic involution hallmarks, which mechanistically links intestinal permeability with immune ageing and immunosenescence¹⁶⁶. Similarly, loss of the commensal bacterium *Akkermansia muciniphila*, driven by activated

Glossary

Age-associated B cells

(ABCs). T-bet⁺CD11c⁺CD21⁺CD23⁺ B cells that expand with age. ABCs arise from antigen-experienced memory B cells and compromise germinal centre reactions, contributing to immunosenescence.

Age-associated CD8⁺ T cells

CD8⁺ memory T cells that are positive for PD1 and granzyme K, indicating that they have an exhausted phenotype and secrete protease that can spread senescence.

B1a B cells

B1a B cells are long-lived innate-like B cells primarily residing in peritoneal cavities. These cells can recognize bacterial and self-antigen, which enables a rapid response to cellular damage and infection.

Brown adipose tissue

In contrast to white adipose tissue, brown adipose tissue is primarily composed of brown adipocytes, which are rich in mitochondria and specialized for non-shivering thermogenesis. However, with ageing, brown adipose tissue progressively lose their identity and acquire white adipose tissue-like characteristics, resulting in impaired thermogenic capacities.

CCR2⁺ monocytes and B1a B cells in the peritoneal cavity, was associated with impaired insulin responses in aged mice and macaques¹⁶⁸. Supplementation with *A. muciniphila* or treatment with the antibiotic enrofloxacin, which increases *A. muciniphila* abundance, restored normal insulin sensitivity¹⁶⁸.

Immunotherapy

Immunotherapy approaches can reverse age-related cellular changes in immune cells and enhance their ability to effectively eliminate senescent cells. For example, pharmacological inhibitors of the cGAS–STING pathway can decrease the senescent cell burden, macrophage infiltration and inflammatory cytokine secretion¹⁴¹. Furthermore, chimeric antigen receptor (CAR) T cells have been engineered to target antigens expressed preferentially on senescent cells such as the

Damage-associated molecular pattern

(DAMP). A class of molecule motif commonly expressed during cellular stress or certain types of cell death. DAMPs activate specific immune responses that are designed to reduce cellular stress.

ERCC1

ERCC1 encodes one of two subunits of a DNA endonuclease that are involved in multiple types of DNA damage repair. Deletions or mutations in these genes have severe effects, ranging from diseases including xeroderma pigmentosum to Cockayne syndrome and cancer.

Exhaustion

A term that is used to describe an inability of a cell to perform a normal function that is due to chronic exposure to activating stimuli in the environment. T cell exhaustion is well described and occurs in the context of chronic T cell receptor stimulation, where prolonged antigen exposure leads to reduced effector function and upregulation of inhibitory receptors.

Innate-like lymphocytes

These cells do not fit into historical classification of adaptive or innate immune cells. Innate-like cells, including natural killer cells, innate lymphoid cells and $\gamma\delta$ T cells, typically have both adaptive and innate-like characteristics and act to bridge innate and adaptive immunity.

Minority mitochondrial outer membrane permeabilization

Mitochondrial outer membrane permeabilization (MOMP) refers to widespread permeabilization of mitochondrial permeabilization in apoptotic cells, whereas minority MOMP occurs only in a subset of mitochondria. This process depends on BAX–BAK macropore formation, which enables the release of mitochondrial DNA into the cytosol, thereby promoting cellular senescence and the secretion of pro-inflammatory cytokines.

Pathogen-associated molecular patterns

Small conserved molecular motifs found in microorganisms but absent in hosts. Pathogen-associated molecular patterns are recognized by immune cells, commonly myeloid or innate cells. These cells express Toll-like receptors and NOD-like receptors, which detect pathogen-associated molecular patterns and initiate immune activation upon encounter.

Secondary senescence

Propagation of senescence that results in non-cell-autonomous induction of secondary senescence.

urokinase-type plasminogen activator receptor (uPAR)¹⁶⁹. Treatment with uPAR-specific CAR T cells in aged mice reduced uPAR-positive and senescence-associated β -galactosidase-positive cells across multiple tissues, decreasing systemic inflammation, improving glucose sensitivity and enhancing physical performance¹⁷⁰. In addition, checkpoint blockade using anti-PD1 or anti-CTLA4 antibodies offers another potential strategy to enhance immune surveillance, improving immunity and promoting the clearance of senescent cells with age^{45–47,171,172}.

Senotherapeutics

Reducing senescent cells, either genetically or pharmacologically, improves healthspan and median lifespan in mouse models. Several senotherapeutic agents, for example, fisetin or the combination of dasatinib and quercetin, are currently in clinical trials for age-related

Senotherapeutic

Senotherapeutics are a class of drugs that target cellular senescence, generally classified into two types: senolytics and senomorphics. Senolytics selectively kill senescent cells, and include dasatinib, quercetin and fisetin. Senomorphics, such as rapamycin, do not kill senescent cells but instead suppress their detrimental effects, including the secretion of senescence-associated secretory phenotypes.

Telomeres

Telomeric DNA is composed of nucleotide repeats that protect the end of chromosomes during replication. Telomere shortening leads to a DNA damage response that can result in induction of senescence, where deposition of DNA repair proteins that form telomere associated foci is a marker for cellular senescence⁵².

TFAM

TFAM encodes mitochondrial transcription factor A, a protein required for the transcription and packaging of mitochondrial DNA. TFAM is essential for mitochondrial biogenesis.

Virtual memory T cells

CD8⁺ T cells that have a memory phenotype but have not been exposed to a specific antigen. Their development is driven by homeostatic proliferation and cytokines. These cells retain the ability to produce cytokines and are increased in numbers in older individuals.

diseases and disorders^{173–176}. Given that immune cells can develop a senescent-like phenotype, it is not surprising that treatment with senotherapeutics improves immune function and extends healthspan^{4,177}. However, it is still not clear if the senotherapeutics directly affect the senescent-like immune cell population or if reducing the overall burden of senescent cells, and thus the circulating SASP, leads to an improvement in immune function. Mouse models in which p16^{Ink4a} and p21^{Cip1} senescent cells can be eliminated in a cell-type-specific and tissue-type-specific manner¹⁷⁸ are needed to determine if reducing the elevated inflammation caused by the increased senescent cell burden is sufficient or if senotherapeutics directly targeting specific immune populations need to be developed.

Partial reprogramming

Expression of four factors – OCT4, SOX2, KLF4 and MYC (OSKM) – can reprogramme differentiated cells into pluripotent stem cells¹⁷⁹. Interestingly, short-term expression of these factors can also lead to partial reprogramming, rejuvenating aged cells at the epigenetic and transcriptomic level without loss of cell identity¹⁸⁰. Delivery of OSKM by viral gene transfer with a regulated promoter or transiently using mRNA transfection has shown evidence of rejuvenation in specific tissues in vivo^{181,182}. Cocktails of small molecules have provided similar rejuvenating results in cell culture¹⁸³. These promising results suggest that partial reprogramming could be applied to improving immune function, possibly through targeting HSCs or progenitor cells with transient expression of OSKM or by treatment with a cocktail of drugs that mimic the effect of OSKM.

Summary

Changes in immune cell function with age contribute not only to dysregulated immune responses but also to systemic ageing. Given this key role of the immune system in ageing, it represents an excellent therapeutic target to improve resilience to infection and disease and to extend healthspan and possibly even lifespan. However, whether the changes in immune function are driven primarily by cell-autonomous changes or are influenced by factors secreted from non-immune cells, such as senescent cells, have not been fully delineated. Despite this lack of knowledge, multiple types of interventions, including diet, microbiota, immunotherapy and senotherapeutics, have had positive effects on the ageing immune system. In addition, new approaches, such as partial rejuvenation of immune cells, have the potential to improve immune function, which, in turn, will extend healthspan. Nonetheless, immune rejuvenation is accompanied by risk for adverse effects such as triggering inappropriate immune activation^{184,185}. Future therapeutic approaches will need to consider immune function from multiple viewpoints, including in the settings of autoimmunity and age-associated infectious diseases.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

P.D.R. and L.J.N. are co-founders of Itasca Therapeutics, developing senolytics to extend healthspan, and have filed patents on senolytic compounds owned by the University of Minnesota.

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