REVIEW PAPER

Immune Ageing: From Cellular Remodelling To Clinical Outcomes

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ABSTRACT
Ageing is associated with profound and progressive alterations in immune structure and function that collectively reshape host defence across the lifespan. These changes, broadly described as immunosenescence, reflect not merely immune decline but a complex remodelling of both innate and adaptive immunity. Immunosenescence contributes to increased susceptibility to infections, diminished vaccine responsiveness, heightened cancer risk, and the paradoxical emergence of chronic inflammatory and autoimmune conditions in older adults. This review integrates current evidence on the biological drivers of immune ageing, focusing on thymic involution, lymphocyte repertoire contraction, cellular senescence, and dysregulated cytokine signalling. Particular attention is given to the clinical implications of these immune alterations and their relevance to infectious disease outcomes, cancer surveillance, and age-associated comorbidities. Emerging therapeutic and preventive strategies, including tailored vaccination approaches and immunomodulatory interventions, are critically examined. Understanding immune ageing as a dynamic and potentially modifiable process provides a foundation for developing integrated strategies to extend health span and improve quality of life in ageing populations.

Keywords: Immunosenescence, immune ageing, thymic involution, therapeutic, ageing immunity, vaccination

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Introduction

Ageing represents a progressive biological process marked by declining physiological resilience and reduced capacity to maintain homeostasis. Although ageing is a universal phenomenon, its molecular and cellular foundations are still being actively elucidated. Contemporary research has identified a set of conserved biological hallmarks—including genomic instability, cellular senescence, altered intercellular communication, and stem cell exhaustion—that collectively drive age-associated functional decline (Campisi, 2013; Lopez-Lluch et al., 2015). Among the physiological systems affected, the immune system undergoes particularly profound and clinically relevant alterations, a process broadly referred to as immunosenescence (Nikolich-Zugich, 2018; Goronzy and Weyand, 2013).

Immune ageing does not reflect a simple loss of function; rather, it involves extensive remodelling of both innate and adaptive immune compartments. These changes arise through intrinsic ageing of immune cells and extrinsic influences from senescent non-immune tissues, which impair barrier integrity and generate a pro-inflammatory signalling milieu (Fulop et al., 2013; Franceschi et al., 2018). The accumulation of senescent cells and their associated senescence-associated secretory phenotype (SASP) further reshapes immune regulation, promoting chronic low-grade inflammation while simultaneously weakening protective immune responses (Rea et al., 2018). As a consequence, immunosenescence contributes to diminished immune surveillance, impaired responses to vaccination, and increased susceptibility to infectious diseases, malignancies, and autoimmune conditions in older adults (Pawelec, 2012; Weyand and Goronzy, 2016).

Importantly, immune dysfunction not only accompanies ageing but actively accelerates systemic decline by compromising tissue repair mechanisms and the clearance of damaged or transformed cells (Nikolich-Zugich, 2018; Lee et al., 2022). Understanding the mechanisms that drive immune ageing is therefore critical for developing targeted interventions aimed at preserving immune competence, reducing disease burden, and promoting healthy longevity in ageing populations (Cisneros et al., 2022; Kumar et al., 2024).

Background

Age-associated immune dysfunction arises from the combined influence of intrinsic biological ageing and cumulative extrinsic exposures, including environmental factors, lifestyle patterns, and chronic antigenic stimulation across the lifespan (Fulop et al., 2013; Pawelec, 2012). One of the earliest and most influential drivers of immune ageing is progressive thymic involution. The thymus, which is central to the development, maturation, and selection of naïve T lymphocytes, undergoes steady atrophy beginning in early adulthood. This structural regression results in a marked reduction in naive T-cell output and a progressive contraction of the T-cell receptor (TCR) repertoire, thereby limiting immune adaptability and weakening responses to newly encountered pathogens (Goronzy and Weyand, 2013; Palmer, 2013).

Concurrently, ageing is accompanied by qualitative shifts in T-cell composition. Peripheral immune compartments become increasingly dominated by long-lived memory and senescent T cells, particularly within the $CD8^+$ subset. These cells exhibit shortened telomeres, diminished proliferative capacity, and altered effector functions, including enhanced secretion of pro-inflammatory mediators (Akbar & Henson, 2011; Hodes

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et al., 2002). The accumulation of these dysfunctional T-cell populations contributes to a persistent, low-grade inflammatory state known as inflammaging, which has been strongly implicated in the development of multiple age-related pathologies, including cardiovascular disease, cancer, and neurodegenerative disorders (Franceschi et al., 2018; Rea et al., 2018).

Humoral immunity is likewise compromised during ageing. Declining B-cell lymphopoiesis within the bone marrow leads to reduced generation of naive B cells, thereby impairing antibody diversity and affinity (Pang et al., 2011; Montecino-Rodriguez et al., 2013). In addition, ageing is associated with defects in class-switch recombination, somatic hypermutation, and plasma cell differentiation, resulting in antibody responses that are quantitatively weaker and qualitatively inferior following infection or vaccination (Frasca et al., 2008; Frasca & Blomberg, 2011; Gupta, 2014). Consequently, older adults exhibit attenuated and less durable humoral immune protection, contributing to reduced vaccine efficacy and increased susceptibility to infectious diseases.

Ageing also profoundly alters innate immune function. Natural killer (NK) cells demonstrate age-related reductions in cytotoxic activity and altered receptor expression, while macrophages increasingly adopt pro-inflammatory phenotypes with impaired phagocytic and antigen-presenting capacities (Solana et al., 2012; Shaw et al., 2010). These changes diminish early pathogen clearance and amplify inflammatory signalling, thereby promoting tissue damage and increasing susceptibility to chronic inflammatory conditions (Hearps et al., 2012).

The clinical consequences of these immune alterations are substantial. Older individuals experience a higher incidence and greater severity of infectious diseases, particularly respiratory infections such as influenza and pneumonia, which are associated with increased morbidity and mortality in ageing populations (Gavazzi and Krause, 2002; Pawelec, 2012). In parallel, impaired immune surveillance facilitates tumour initiation and progression, contributing to the rising cancer burden observed with advancing age (Weyand and Goronzy, 2016; Boccardi and Marano, 2024). Furthermore, immune dysregulation during ageing increases the risk of autoimmune disorders, characterised by loss of self-tolerance and inappropriate immune activation against host tissues (Weyand and Goronzy, 2020).

Given the broad health impact of immunosenescence, targeted strategies to counteract age-related immune decline are essential. Accordingly, this review explores emerging and established interventions—including optimised vaccination strategies, immunomodulatory therapies—aimed at preserving immune competence and improving health outcomes in older adults (Doherty et al., 2025; Kumar et al., 2024).

Mechanisms of Immunosenescence

Immune ageing, commonly referred to as immunosenescence, reflects a complex remodelling of immune architecture that affects both innate and adaptive defence mechanisms (Iordache et al., 2024). Rather than representing a uniform loss of immune function, immunosenescence involves coordinated changes in immune cell composition, functional capacity, and regulatory networks that collectively reshape host defence across the lifespan (Nikolich-Zugich, 2018; Lee et al., 2022). These alterations are influenced by a wide range of interacting factors, including genetic background, nutritional status, biological sex, physical activity, ethnicity, and cumulative exposure to infectious agents, underscoring the need for a systems-level understanding of immune ageing (Fulop et al., 2018; Cisneros et al., 2022).

Beyond intrinsic immune cell ageing, deterioration of physical barrier defences represents an important yet often under-recognised contributor to immunosenescence. In older individuals, age-related structural and functional changes in the skin—including thinning of the epidermis, reduced hydration, and diminished production of antimicrobial peptides—compromise its protective function and increase susceptibility to microbial invasion (Solana et al., 2012; Chidrawar et al., 2006). Similarly, ageing of mucosal surfaces is associated with impaired ciliary clearance and altered chemokine expression, facilitating microbial adherence, colonisation, and persistence at epithelial interfaces (Shaw et al., 2010; Chidrawar et al., 2006).

Thymic Atrophy and Loss of the Naive T-Cell Repertoire: Thymic involution is a defining hallmark of immunosenescence and represents a multifactorial process involving progressive anatomical, cellular, and functional alterations within the thymus. As the primary lymphoid organ responsible for generating a diverse and self-tolerant T-cell repertoire, the thymus plays a central role in sustaining adaptive immune competence throughout life. Contrary to earlier assumptions that thymic function becomes largely redundant in adulthood, accumulating evidence indicates that continued thymic output is essential for maintaining peripheral T-cell receptor (TCR) diversity and immune responsiveness under both physiological and pathological conditions (Palmer, 2013; Cardinale et al., 2021).

With advancing age, thymic architecture undergoes gradual disorganisation characterised by cortical and medullary shrinkage, loss of thymic epithelial cells, and replacement of functional tissue with adipose deposits. These structural changes markedly impair the thymic microenvironment required for effective thymocyte maturation and selection (Palmer, 2013; Aw et al., 2020). As thymic involution progresses, the production of naive T cells declines sharply, resulting in progressive restriction of the peripheral TCR repertoire and reduced capacity to respond to novel antigens.

In parallel, peripheral immune compartments become increasingly dominated by antigen-experienced memory and senescent T cells. These cells frequently exhibit shortened telomeres, loss of co-stimulatory molecules such as CD28, diminished proliferative potential, and enhanced secretion of pro-inflammatory cytokines, thereby contributing to chronic inflammatory signalling and impaired immune surveillance (Hodes et al., 2002;

Akbar and Henson, 2011). Collectively, these changes weaken host defence against emerging infections, compromise vaccine-induced immunity, and facilitate immune evasion by malignant cells (Weyand and Goronzy, 2016; Pawelec, 2012).

Multiple molecular and cellular mechanisms contribute to thymic ageing, including functional decline of thymic epithelial cells, reduced production of thymic hormones such as thymosin, increased oxidative stress, and chronic inflammatory signalling within the thymic niche. These processes collectively limit thymic regenerative capacity and accelerate age-associated immune dysfunction (Palmer, 2013; Aw et al., 2020; Chervova et al., 2024).

Given its central role in shaping adaptive immunity, thymic involution represents an attractive therapeutic target in strategies aimed at counteracting immunosenescence. While current approaches—such as enhanced vaccine adjuvants—may partially compensate for reduced naïve T-cell output, emerging regenerative strategies, including thymic bioengineering and artificial thymic organoids, hold promise for restoring thymopoiesis and improving immune resilience in ageing populations (Bredenkamp et al., 2014; Seet et al., 2017)

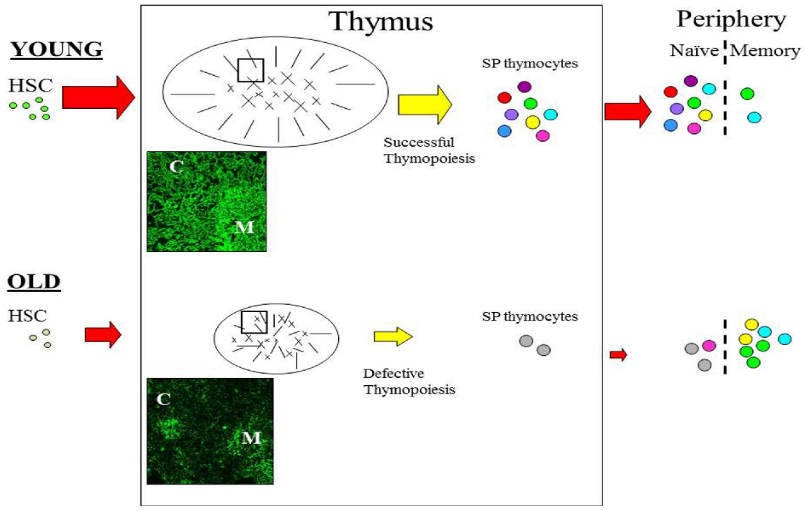

Figure 1: The Effect of Age on Thymic Function. This schematic diagram illustrates the pathway of T-cell development and the influence of aging on thymic function. (Source: https://doi.org/10.3389/fimmu.2013.00316)

Lymphocyte Dysfunction and Repertoire Contraction

Ageing exerts profound effects on lymphocyte generation, maintenance, and functional integrity, resulting in a progressive restriction of immune diversity and reduced adaptability to novel antigens. One of the central drivers of this process is age-associated alteration in haematopoietic stem cell (HSC) biology. With advancing age, HSCs exhibit reduced self-renewal capacity and an intrinsic bias toward myeloid lineage differentiation at the expense of lymphopoiesis, leading to diminished production of lymphoid progenitors (Pang et al., 2011; Montecino-Rodriguez et al., 2013). This shift contributes to sustained deficits in both B- and T-cell compartments.

B-Cell Dysfunction in Ageing in the bone marrow, declining lymphoid output results in a reduced influx of naïve B cells into the peripheral circulation, thereby constricting the available B-cell receptor (BCR) repertoire (Gibson et al., 2009). Ageing is further associated with expansion of oligoclonal, antigen-experienced B-cell populations, which dominate the peripheral B-cell pool and limit responsiveness to newly encountered pathogens (Frasca et al., 2008a; Frasca et al., 2008b).

Functional impairments in aged B cells exacerbate these quantitative deficits. Age-related downregulation of key transcription factors, including E2A, and reduced expression of activation-induced cytidine deaminase (AID) impair class-switch recombination and somatic hypermutation, leading to reduced generation of high-affinity, class-switched antibodies (Frasca et al., 2008b). Consequently, antibody responses in older individuals are not only diminished in magnitude but also exhibit reduced specificity and durability following infection or vaccination (Frasca and Blomberg, 2011).

Defective intracellular signalling pathways further compromise B-cell activation, proliferation, and differentiation into long-lived plasma cells and memory B cells. These alterations collectively contribute to impaired humoral immunity and reduced vaccine efficacy in ageing populations (Gupta, 2014).

T-Cell Dysfunction and Repertoire Contraction: T-cell immunity undergoes equally profound remodelling with age. Progressive thymic involution limits the continuous generation of naïve T lymphocytes, resulting in contraction of the peripheral T-cell receptor (TCR) repertoire and diminished immunological flexibility (Palmer, 2013; Aw et al., 2020). As naive T-cell numbers decline, peripheral compartments become increasingly populated by memory and terminally differentiated effector T cells, particularly within the $CD8^{+}$ subset (Fulop et al., 2013; Pawelec, 2012).

At the cellular level, ageing T cells exhibit hallmark features of replicative senescence, including telomere shortening, reduced telomerase activity, diminished proliferative capacity, and altered metabolic profiles (Hodes et al., 2002; Fali et al., 2019). Senescent T cells frequently lose expression of co-stimulatory molecules such as CD28 while acquiring enhanced pro-inflammatory secretory capacity, thereby contributing to chronic low-grade inflammation and immune dysregulation (Akbar and Henson, 2011; Weyand and Goronzy, 2020).

Persistent antigenic stimulation—particularly from latent viral infections—further accelerates T-cell exhaustion and repertoire skewing, reinforcing immune imbalance in older adults (Fulop et al., 2013). Collectively, these changes impair coordinated immune responses, weaken pathogen clearance, and reduce the effectiveness of vaccine-induced immunity (Goronzy & Weyand, 2013; Nikolich-Zugich, 2018).

Telomere Dynamics and Lymphocyte Ageing: Telomere attrition represents a unifying molecular mechanism underlying lymphocyte ageing. Progressive telomere shortening limits replicative potential and promotes senescence in both T and B cells, thereby constraining immune renewal and long-term immune competence (Hodes et al., 2002; Sahin et al., 2011). Genetic, environmental, and lifestyle factors further modulate telomere dynamics, contributing to inter-individual variability in immune ageing trajectories (Gold et al., 2024).

Innate Immune Dysregulation and Inflammaging

Ageing exerts a profound impact on the innate immune system, leading to functional decline across multiple innate immune cell populations and contributing substantially to immunosenescence. Innate immune cells—including macrophages, neutrophils, monocytes, dendritic cells, and natural killer (NK) cells—exhibit age-associated alterations in phenotype, signalling capacity, and effector function that collectively impair early pathogen recognition and clearance (Shaw et al., 2010; Solana et al., 2012).

Macrophage and Monocyte Dysfunction: Macrophages play a central role in innate immunity through pathogen recognition, phagocytosis, antigen presentation, and cytokine production. With ageing, macrophages demonstrate reduced phagocytic efficiency and impaired production of key cytokines required for effective immune activation (Hearps et al., 2012). In parallel, ageing is associated with decreased expression and signalling of pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), leading to diminished microbial sensing and delayed immune responses (Shaw et al., 2010).

Monocytes from older individuals frequently display dysregulated activation states and skewed cytokine profiles characterised by heightened basal inflammatory signalling. This chronic activation contributes to systemic inflammation and disrupts immune homeostasis, thereby exacerbating tissue damage and impairing host defence (Hearps et al., 2012; Rea et al., 2018).

Neutrophil Dysfunction Neutrophils constitute the first line of defence against bacterial and fungal infections; however, ageing markedly compromises their functional capacity. Age-associated defects include reduced chemotaxis, impaired phagocytosis, diminished production of reactive oxygen species (ROS), and altered formation of neutrophil extracellular traps (NETs). These changes limit the ability of neutrophils to efficiently eliminate pathogens and are closely linked to increased morbidity and mortality from infectious diseases in older adults (Gavazzi and Krause, 2002; Solana et al., 2012).

Natural Killer Cell Alterations: Natural killer (NK) cells are critical for early antiviral defence and tumour surveillance. Although total NK cell numbers may be preserved or even increased with age, their functional competence declines significantly. Ageing is associated with reduced cytotoxic activity, impaired degranulation, and altered cytokine secretion profiles, including decreased interferon-gamma (IFN-γ) production (Le Garff-Tavernier et al., 2010; Gavazzi and Krause, 2002).

Phenotypic remodelling of NK cell subsets is a hallmark of immune ageing. The proportion of less mature CD56 bright NK cells increases, while the more cytotoxic CD56 dim subset declines, resulting in reduced tumour- and virus-targeting efficiency (Le Garff-Tavernier et al., 2010). In addition, aged NK cells exhibit shortened telomeres, reduced telomerase activity, impaired proliferative responses to cytokine stimulation, and increased expression of inhibitory receptors such as killer cell immunoglobulin-like receptors (KIRs), further limiting their effector function (Fali et al., 2019; Borrego, 2013; Gomez-Lopez et al., 2017).

Age-related alterations in the cytokine milieu also contribute to impaired NK cell function. Declining levels of interleukin-2 (IL-2) and interleukin-15 (IL-15), which are essential for NK cell development and survival, reduce NK cell responsiveness, while elevated levels of inflammatory mediators such as interleukin-6 (IL-6) and growth differentiation factor-15 (GDF15) reinforce an inhibitory inflammatory microenvironment (Rea et al., 2018; Le Garff-Tavernier et al., 2010). Nevertheless, in vitro studies demonstrate that stimulation with IL-2, IL-12, IL-15, or interferon-α can partially restore NK cell cytotoxicity, highlighting the therapeutic potential of cytokine-based immune modulation (Tomescu et al., 2009).

Inflammaging and Altered Cytokine Networks: A defining feature of innate immune ageing is the emergence of a chronic, low-grade inflammatory state termed inflammaging. This condition is characterised by persistently elevated circulating levels of pro-inflammatory mediators, including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and C-reactive protein (CRP), in the absence of overt infection (Franceschi et al., 2018; Rea et al., 2018).

Inflammaging arises from multiple converging mechanisms, including accumulation of senescent cells with a senescence-associated secretory phenotype

(SASP), mitochondrial dysfunction, impaired autophagy, and chronic activation of innate immune signalling pathways such as NF-κB and inflammasome cascades (Campisi, 2013; Di Micco et al., 2021). While low-level inflammation may initially serve adaptive purposes, persistent inflammaging promotes tissue degeneration, disrupts immune regulation, and drives the pathogenesis of numerous age-related diseases, including cardiovascular disease, neurodegeneration, metabolic disorders, and cancer (Franceschi et al., 2018; Boccardi & Marano, 2024).

Collectively, dysregulation of innate immune function and chronic inflammatory signalling significantly weaken host defence, reduce vaccine responsiveness, and accelerate systemic ageing. These changes underscore the importance of therapeutic strategies aimed at restoring innate immune balance and attenuating inflammaging to preserve immune competence in older adults

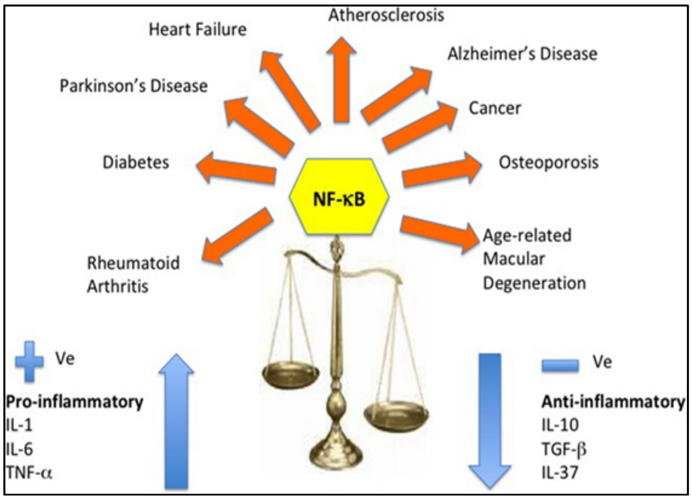

Figure 2. Several molecular pathways have been identified that trigger the inflammasome and stimulate the NF-κB and the IL-1β-mediated inflammatory cascade of cytokines. (Source: https://doi.org/10.3389/fimmu.2018.00586).

Clinical Implications of Immunosenescence

The progressive deterioration of immune competence with ageing has far-reaching clinical consequences that significantly impact morbidity, mortality, and quality of life in older adults. Immunosenescence compromises both protective immunity and immune regulation, thereby increasing susceptibility to infectious diseases, malignancies, and immune-mediated disorders while simultaneously reducing the effectiveness of preventive and therapeutic interventions (Pawelec, 2012).

Increased Susceptibility to Infectious Diseases Older adults experience a disproportionate burden of infectious diseases, characterised by higher incidence rates, increased disease severity, prolonged recovery, and elevated mortality. Respiratory infections, including influenza, pneumonia, and more recently COVID-19, represent a major cause of hospitalisation and death in ageing populations (Gavazzi and Krause, 2002; Pawelec, 2012). Age-related impairments in innate immune recognition, delayed adaptive immune activation, and reduced immune memory formation collectively weaken pathogen clearance and increase vulnerability to both primary infections and reinfections (Fulop et al., 2013; Shaw et al., 2010).

In addition to intrinsic immune defects, inflammaging contributes to dysregulated immune responses during infection, often resulting in excessive tissue damage and impaired resolution of inflammation. This maladaptive inflammatory response has been implicated in the heightened severity of infectious diseases observed in older individuals, particularly during viral respiratory infections (Franceschi et al., 2018; Rea et al., 2018).

Reduced Vaccine Efficacy: Vaccination remains one of the most effective strategies for preventing infectious diseases; however, vaccine-induced protection is frequently reduced in older adults. Immunosenescence limits vaccine efficacy through diminished antigen presentation, impaired T- and B-cell activation, restricted lymphocyte repertoire diversity, and defective generation of long-lived immune memory (Goronzy and Weyand, 2013; Frasca and Blomberg, 2011). As a result, older individuals often exhibit lower seroconversion rates, reduced antibody titres, and shorter duration of protection following vaccination compared with younger populations (Gupta, 2014; Pawelec, 2012).

These limitations have prompted the development of tailored vaccination strategies for older adults, including high-dose antigen formulations, enhanced adjuvants, and alternative delivery platforms designed to overcome age-related immune deficits (DiazGranados et al., 2014; Izurieta et al., 2015). While such approaches have improved vaccine responsiveness, immune protection in frail and very old individuals remains suboptimal, highlighting the need for further innovation.

Cancer and Impaired Immune Surveillance: Effective immune surveillance is essential for the detection and elimination of malignant cells. With ageing, impaired function of cytotoxic T lymphocytes and natural killer (NK) cells compromises tumour immunosurveillance, facilitating cancer initiation and progression (Weyand & Goronzy, 2016; Borrego, 2013). Chronic inflammation further promotes tumourigenesis by creating a pro-tumorigenic microenvironment characterised by sustained cytokine signalling, oxidative stress, and genomic instability (Franceschi et al., 2018; Boccardi and Marano, 2024).

In addition, age-related immune dysfunction limits the efficacy of cancer immunotherapies, including immune checkpoint inhibitors, as older patients may exhibit reduced T-cell responsiveness and altered immune regulation (Weyand and Goronzy, 2020). These challenges underscore the importance of age-adapted immunotherapeutic strategies and careful consideration of immune ageing in oncology care.

Autoimmunity and Chronic Inflammatory Conditions Paradoxically, immunosenescence is associated not only with immune deficiency but also with increased risk of autoimmune and chronic inflammatory disorders. Age-related defects in central and peripheral tolerance mechanisms, coupled with expansion of autoreactive lymphocyte clones, contribute to loss of self-tolerance and inappropriate immune activation against host tissues (Weyand and Goronzy, 2020). Chronic inflammaging further amplifies autoimmune pathology by sustaining inflammatory signalling and tissue damage (Rea et al., 2018).

Moreover, immune dysregulation in ageing has been linked to the pathogenesis of multiple non-communicable diseases, including cardiovascular disease, type 2 diabetes, osteoporosis, and neurodegenerative disorders, in which chronic inflammation plays a central role (Franceschi et al., 2018; Di Micco et al., 2021).

Collectively, these clinical manifestations highlight immunosenescence as a central driver of age-related disease vulnerability. Addressing immune ageing through targeted interventions is therefore essential not only for infection prevention but also for reducing the broader disease burden associated with ageing.

Therapeutic and Preventive Strategies Against Immunosenescence

Trained vaccination protocols, novel immunomodulatory therapies, and lifestyle interventions are critical to addressing immunosenescence in the elderly and mitigating its clinical consequences (Nikolich-Zugich, 2018; Cisneros et al., 2022).

Tailored Vaccination Protocols

High-Dose Vaccines: High-dose influenza vaccines have demonstrated increased efficacy in older adults by eliciting stronger humoral and cellular immune responses compared with standard-dose formulations (DiazGranados et al., 2014). Additionally, the COVID-19 pandemic highlighted the heightened vulnerability of older adults to respiratory infections and marked the first widespread clinical application of mRNA vaccine technology. The two leading mRNA COVID-19 vaccines, based on nucleoside-modified mRNA encoding an optimised SARS-CoV-2 spike protein, induced robust T-cell and B-cell responses in older adults, although immune responses were weaker than those observed in younger individuals, with frail populations exhibiting the lowest responsiveness (Walsh et al., 2020; Doherty et al., 2025).

Adjuvanted Vaccines: Vaccines formulated with adjuvants, such as the MF59-adjuvanted influenza vaccine, enhance immune responses by improving antigen presentation and promoting stronger and more durable immunity in older adults (Vesikari et al., 2011).

Booster Doses: Regular booster vaccinations can help sustain protective immunity in ageing populations, particularly for vaccines such as tetanus, diphtheria, pertussis (Tdap), and pneumococcal vaccines, where immune memory may wane with age (Goronzy and Weyand, 2013; Pawelec, 2012).

Immunomodulatory Therapies In the context of age-related immune system changes, immunomodulatory therapy aims to counteract immunosenescence—the progressive decline in immune function associated with ageing. Emerging immunomodulatory strategies designed to address age-related immune dysfunction are summarised in Table 1. These approaches seek to restore immune competence and reduce chronic inflammation through targeted modulation of key biological pathways (Cisneros et al., 2022; Kumar et al., 2024).

Proposed interventions include epigenetic programming, which targets age-associated alterations in DNA methylation and histone modifications to rejuvenate immune cell function (Moskalev et al., 2017; Shah et al., 2016). Metabolic reprogramming, using caloric restriction mimetics and metformin, aims to enhance immune metabolism and reduce inflammatory signalling (Madeo et al., 2019; Barzilai et al., 2016). Mitochondrial enhancement strategies focus on stimulating mitochondrial biogenesis and employing mitochondria-targeted antioxidants to mitigate oxidative stress and improve immune cell energetics (Lopez-Lluch et al., 2015; Smith and Murphy, 2010; Camacho-Ensina et al., 2024).

Additional approaches include senescence-associated secretory phenotype (SASP) modulation, which seeks to inhibit or alter the pro-inflammatory secretions of senescent cells (Campisi and d'Adda di Fagagna, 2007; Di Micco et al., 2021), and autophagy enhancement, achieved through pharmacological induction or agents such as rapamycin to promote cellular quality control and immune homeostasis (Rubinsztein et al., 2011; Wilkinson et al., 2012). Artificial thymic organoids represent a regenerative strategy aimed at restoring thymic function and T-cell development in ageing individuals (Bredenkamp et al., 2014; Seet et al., 2017). Finally, redox modulation, through redox-active compounds and Nrf2 pathway activation, is proposed to strengthen antioxidant defences and reduce age-associated inflammation (Velarde et al., 2012; Martini and Passos, 2023).

Together, these immunomodulatory strategies provide a comprehensive roadmap for rejuvenating immune function and mitigating the detrimental effects of immunosenescence in older adults

Table 1. Innovative Immunomodulatory Strategies to Counteract Immuno-senescence

S. No.	Intervention Strategy	Core Mechanism / Rationale	References (Author–Year)
1	Epigenetic Rejuvenation Approaches	DNA methylation modulation: Reprogramming age-associated DNA methylation patterns to restore functional competence of immune cells	Shah et al., 2016; Ahmad et al., 2024
		Histone modification targeting: Regulating histone marks to re-establish youthful transcriptional profiles in immune populations	Moskalev et al., 2017
2	Immune Metabolic Modulation	Caloric restriction mimetics: Pharmacological agents that replicate caloric restriction effects to enhance immune resilience	Madeo et al., 2019
		Metformin therapy: Repurposing metformin to optimise immune cell metabolism and functional responses	Barzilai et al., 2016
3	Mitochondrial Function Optimisation	Induction of mitochondrial biogenesis: Stimulating the generation of new mitochondria to improve bioenergetic capacity of immune cells	Lopez-Lluch et al., 2015
		Mitochondria-targeted antioxidants: Limiting mitochondrial oxidative damage to preserve immune cell performance	Smith & Murphy, 2010
4	Regulation of Senescence-Associated Inflammation	SASP suppression: Pharmacological inhibition of pro-inflammatory factors secreted by senescent cells	Di Micco et al., 2021
		Senomorphic agents: Altering senescent cell behaviour to reduce deleterious inflammatory signalling without cell elimination	Campisi & d'Adda di Fagagna, 2007; Zhao et al., 2024
5	Autophagic Pathway Activation	Autophagy enhancers: Promoting intracellular clearance of damaged components to maintain immune cell homeostasis	Rubinsztein et al., 2011
		mTOR inhibition (Rapamycin): Utilising rapamycin and related compounds to stimulate autophagy and improve immune regulation	Wilkinson et al., 2012
6	Thymic Regeneration Technologies	Artificial thymic organoids: Engineering thymus-like structures to support T-cell maturation and immune rejuvenation	Seet et al., 2017
		Bioengineered thymic tissue: Development of transplantable thymic constructs to restore thymopoiesis	Bredenkamp et al., 2014
7	Redox Homeostasis Regulation	Redox-modulating agents: Compounds that balance intracellular redox states to enhance immune cell function	Velarde et al., 2012
		Nrf2 pathway activation: Stimulating Nrf2 signalling to strengthen antioxidant defences and attenuate inflammation	Baker et al., 2011; Cordero et al., 2024

Outcome

The outcome of this review reveals that immunosenescence represents a multifaceted remodelling of both innate and adaptive immunity, leading to increased susceptibility to infections, cancer, and autoimmune diseases in older adults (Lee et al., 2022; Cisneros et al., 2022). A key consequence of immune ageing is reduced vaccine responsiveness, underscoring the importance of tailored strategies such as high-dose, adjuvanted, and mRNA-based vaccines to improve protective efficacy in ageing populations (DiazGranados et al., 2014; Walsh et al., 2020; Doherty et al., 2025). The chronic inflammatory state of "inflammaging" further accelerates age-related comorbidities and systemic functional decline (Franceschi et al., 2018; Rea et al., 2018). Emerging immunomodulatory approaches—including senolytic therapies, metabolic reprogramming, and thymic bioengineering—show considerable promise in mitigating or partially reversing age-associated immune decline (Baker et al., 2011; Madeo et al., 2019; Seet et al., 2017; Bredenkamp et al., 2014; Corveleyn et al., 2024). In addition, lifestyle-based interventions such as antioxidant-rich diets, regular physical activity, stress reduction, and adequate sleep have been shown to buffer immune ageing by reducing chronic inflammation and enhancing immune resilience (Vasto et al., 2014; Joyner, 2011; Sharma and Mehdi, 2023). Collectively, these findings underscore that an integrated strategy—combining optimised vaccination approaches, targeted immunotherapeutics, and lifestyle modifications—is essential to extend healthspan and mitigate the growing burden of ageing-related immune dysfunction (Nikolich-Zugich, 2018; Kumar et al., 2024).

Conclusion

Addressing immunosenescence requires mechanistically informed interventions that not only mitigate functional decline but also promote immune rejuvenation. Emerging strategies such as epigenetic reprogramming, metabolic modulation, mitochondrial restoration, autophagy enhancement, and thymic bioengineering hold translational potential for restoring immune competence. Coupled with tailored vaccination protocols and next-generation immunomodulatory therapeutics, these approaches may recalibrate age-associated immune dysfunction. Future progress will depend on integrating systems immunology, biomarker discovery, and longitudinal clinical studies to delineate causal mechanisms and optimise personalised interventions. Thus, targeting immunosenescence is not only central to improving vaccine responsiveness and infection control in older adults but also represents a critical frontier in extending healthspan and delaying the onset of age-related pathologies.

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Author's Contribution
DK: Conceptualisation, Writing- Original Draft, Visualisation.

Conflict of Interest
No conflict of interest

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