Age-Related Changes in the Immune System

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ABSTRACT

This review examines the concept of immunosenescence, the gradual decline of the immune system associated with ageing, and its extensive effects on health and disease management in elderly individuals. Immunosenescence is marked by reduced efficiency of both innate and adaptive immune responses, leading to increased vulnerability to infections, higher incidence of cancers, and greater susceptibility to autoimmune diseases. Key mechanisms discussed include thymic involution, alterations in T-cell and B-cell populations, and functional changes in the innate immune system. The review also highlights the clinical implications of these immune alterations, particularly the elevated risk of infectious illnesses such as influenza and COVID-19, as well as cancer and autoimmune disorders. Potential approaches to mitigate these effects are explored, including optimised vaccination strategies, novel immunomodulatory therapies, and lifestyle interventions aimed at preserving immune function. Together, these insights underscore the importance of integrated healthcare strategies in supporting healthy ageing and enhancing the quality of life for older adults.

Keywords: Immunosenescence, ageing, immune system, thymic involution, inflammaging, immunomodulation.

1. Introduction

Ageing is characterised by a gradual decline in physiological function. Our understanding of the ageing process remains limited. While its underlying biological causes are largely unknown, research over the past decades has identified common cellular and molecular features linked to ageing. The ageing process is associated with a myriad of physiological changes, among which the decline in immune function, termed immunosenescence, is particularly significant. As ageing impacts virtually all bodily systems, the immune system is no exception. The age-related changes observed in immunity, collectively termed immunosenescence, arise from two complementary processes: the direct senescence of immune cells and the indirect effects of tissue cellular senescence, which

compromises physiological barriers and promotes the release of signalling molecules that influence immune function.[1] Given the critical role of immunity in maintaining homeostasis and clearing damaged cells, it is unsurprising that immunosenescence not only results from ageing but also accelerates the decline of overall organismal function. Immunosenescence encompasses a broad spectrum of alterations in both the innate and adaptive immune systems, leading to increased vulnerability to infections, malignancies, and autoimmune diseases.[1] This review aims to provide a comprehensive overview of the mechanisms underlying immunosenescence and its implications for health and disease management in the elderly.

1.1 Background

As individuals age, the immune system undergoes significant changes that affect its efficacy. These changes are a consequence of both intrinsic factors, such as genetic predispositions, and extrinsic factors, including environmental exposures and lifestyle choices. One of the most prominent features of immunosenescence is the involution of the thymus, an organ essential for the maturation of T cells. The thymus reaches its peak size during adolescence and then progressively atrophies, leading to a decreased output of naive T cells and a reduced T-cell receptor (TCR) repertoire diversity. This decline impairs the body's ability to respond effectively to novel antigens. [1, 2] In addition to thymic involution, there is a notable shift in T-cell populations. Older adults exhibit an accumulation of memory and senescent T cells, particularly CD8+ T cells, characterised by a reduced proliferative capacity and increased production of pro-inflammatory cytokines. This shift contributes to a state of chronic low-grade inflammation, commonly referred to as inflammaging, which is associated with various age-related diseases.[3,4] B cells, responsible for antibody production, also exhibit age-related changes. There is a decline in B-cell lymphopoiesis, leading to a reduced production of naive B cells. Consequently, the elderly have diminished antibody responses to infections and vaccinations, compromising their ability to mount effective immune responses.[5] The innate immune system is similarly affected by ageing. Natural killer (NK) cell activity decreases, and macrophages shift towards a pro-inflammatory phenotype. These alterations contribute to a reduced capacity to eliminate pathogens and an increased risk of chronic inflammatory conditions.[6] The clinical implications of immunosenescence are profound. Older adults are more susceptible to infectious diseases, with higher morbidity and mortality rates. For instance, the elderly population experiences increased severity and complications from respiratory infections such as influenza and pneumonia.[7] The decline in immune surveillance also elevates the risk of cancer development and progression.[8] Additionally, the dysregulation of immune

responses in ageing leads to a higher incidence of autoimmune diseases, where the immune system erroneously targets the body's tissues.[9]

Given the impact of immunosenescence on health, effective strategies for managing age-related immune decline are crucial. This review examines potential interventions, including enhanced vaccination strategies, immunomodulatory therapies, and lifestyle modifications, aimed at preserving immune function and enhancing health outcomes in the elderly.

2. Mechanisms of Immunosenescence

Immunosenescence, the age-related decline in immune function, is characterised by profound changes across both the innate and adaptive immune systems. This review synthesises current knowledge from peer-reviewed studies to elucidate the underlying mechanisms contributing to immunosenescence, focusing on thymic involution, alterations in T-cell and B-cell populations, and changes in the innate immune system. The determinants of immunosenescence are multifactorial, encompassing genetics, nutrition, sex, race, physical activity, and lifetime exposure to pathogens. A comprehensive understanding of this process requires consideration of the physiological alterations that accompany ageing and directly influence immune competence. The body’s physical barriers, serving as the first line of defence, undergo notable age-related changes. In older adults, the skin becomes thinner and drier, leading to a reduction in fat-soluble defensins that normally contribute to antimicrobial protection. Similarly, mucosal barriers lose efficiency with age due to impaired ciliary function, thereby reducing their clearance capacity and facilitating the colonisation and persistence of pathogens. [56]

2.1 Thymic Atrophy and Loss of Naive T-Cell Repertoire

Thymic involution, a hallmark of immunosenescence, is a complex process involving structural, functional, and cellular changes in the thymus gland that significantly impact immune function with ageing. The thymus is the primary lymphoid organ responsible for generating and sustaining a broadly diverse pool of T cells capable of recognising both tumour and pathogenic antigens. Although once thought to play only a marginal role in adult immune competence, the adult thymus is now recognised as crucial for maintaining peripheral TCR repertoire diversity under both physiological and clinical conditions. Thymic function and T-cell output are highly dynamic processes that can be profoundly affected by acute immunological insults—such as infections, stress, or antineoplastic therapies—as well as by chronic dysfunctions, including age-associated involution and recurrent infections.[57] Key

features include the structural changes in the thymus with age, the decline in thymic output, and the impact on T-cell diversity and function in ageing individuals (Figure 1). The thymus gland, crucial for T-cell maturation and development of a diverse T-cell receptor (TCR) repertoire, undergoes progressive atrophy and structural changes during ageing. In early life, the thymus is a primary site where immature T cells (thymocytes) migrate from the bone marrow and undergo selection processes to become mature, functional T cells capable of recognising and responding to specific antigens. However, with advancing age, the thymus gradually loses its structural integrity, characterised by a decline in cortical and medullary compartments, reduced epithelial cell density, and increased adipose tissue infiltration.[10] Thymic involution leads to a marked reduction in the thymic output of naive T cells, which are critical for maintaining a diverse and responsive immune system. Naive T cells are crucial for recognising new pathogens and mounting effective immune responses, particularly through their diverse TCR repertoire. The decline in thymic function results in fewer naive T cells entering the peripheral circulation, leading to a contraction of the TCR repertoire and an accumulation of memory and senescent T cells.[1] This shift contributes to reduced immune surveillance and responsiveness to novel antigens, thereby increasing susceptibility to infections and impairing vaccine responses in older adults. Several cellular and molecular mechanisms underlie thymic involution. These include thymic epithelial cell function alterations, reduced production of thymic hormones like thymopoietin and thymosin, and dysregulation of signalling pathways involved in thymocyte maturation and survival.[10] Age-related changes in the microenvironment of the thymus, such as increased oxidative stress and inflammation, further exacerbate thymic atrophy and impair its regenerative capacity. Understanding thymic involution is crucial for developing strategies to mitigate its effects on immune function in ageing. Additionally, optimising vaccination strategies, particularly through the use of adjuvants or antigen-presenting cell therapies, aims to enhance immune responses in older adults with compromised thymic function. Thymic involution is a central feature of immunosenescence, contributing significantly to the age-related decline in immune function observed in older adults. Elucidating the mechanisms driving thymic atrophy and exploring interventions to preserve or restore thymic function is critical for enhancing immune health and improving vaccine efficacy in ageing populations. Overall, the reduction in thymic functionality and the decline in peripheral T-cell diversity are major contributors to the weakened immune surveillance seen in the elderly, creating a permissive environment for infections and tumours to evade T-cell–mediated responses. Although a temporal correlation

exists, the direct link between diminished thymic function and the rising incidence of cancer with age remains a subject of ongoing debate. [57]

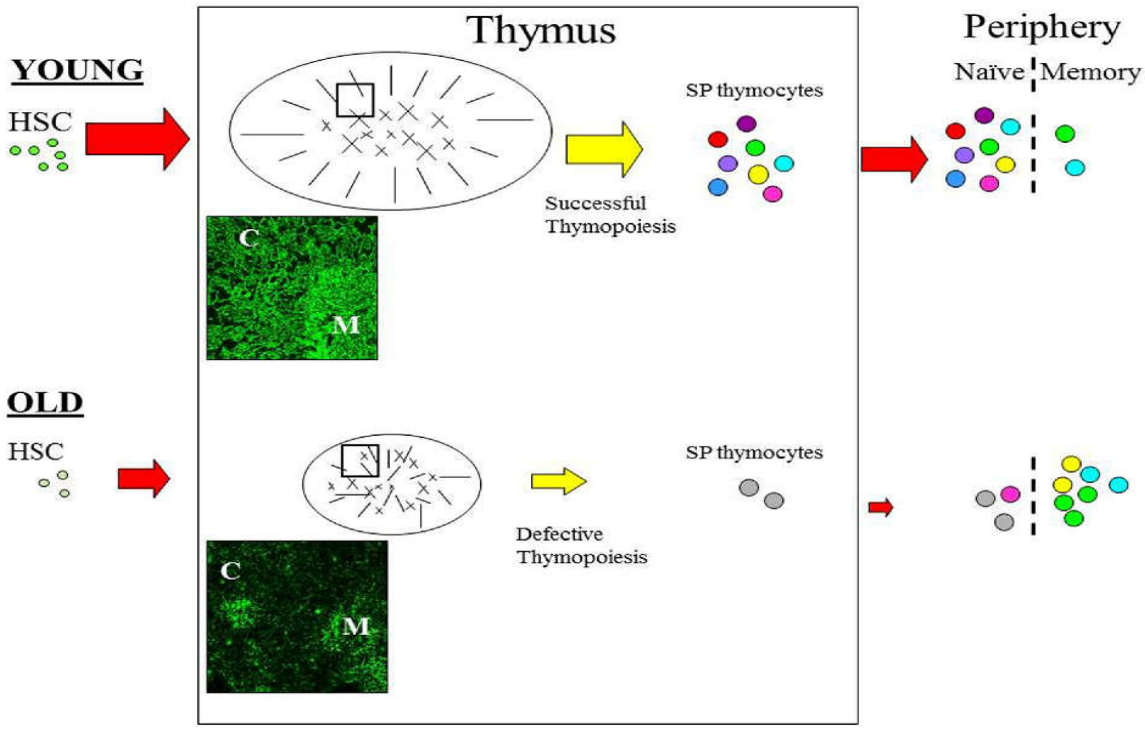

Figure 1: The Effect of Age on Thymic Function. This schematic diagram illustrates the pathway of T-cell development and the influence of aging on thymic function.[11] (Source: https://doi.org/10.3389/fimmu.2013.00316)

2.2 Lymphocyte Dysfunction and Repertoire Constriction

The bone marrow's ability to produce new B-cells declines with age. Hematopoietic stem cells (HSCs) exhibit reduced functionality and a bias towards myeloid over lymphoid lineages.[12] There is a decrease in the number of B-cell precursors, leading to fewer naive B-cells entering the circulation.[13] With age, there is an increased frequency of clonal expansions of B-cells. This results in a narrower B-cell receptor (BCR) repertoire, limiting the ability to respond to new antigens.[14] Age-associated defects in class switch recombination (CSR) impair the ability of B-cells to produce different antibody isotypes, particularly IgG and IgA.[15] B-cells from older individuals produce lower amounts of antibodies, and these antibodies often have a lower

affinity for antigens.[16] B-cells in the elderly show impaired activation and signalling, which can affect their ability to proliferate and differentiate into plasma cells or memory B-cells.[17]

Aging leads to significant changes in T-cell populations, contributing to immunosenescence. The thymus undergoes atrophy, reducing the production of naïve T-cells and resulting in a less diverse T-cell receptor repertoire.[11] This decline in naïve T-cells, coupled with an accumulation of memory T-cells, particularly effector memory T-cells, skews the T-cell repertoire and contributes to chronic inflammation.[2] Ageing T-cells also exhibit reduced proliferative capacity due to telomere shortening and an increased presence of senescent T-cells, which produce pro-inflammatory cytokines and lose the expression of co-stimulatory molecules like CD28.[18, 19] These alterations impair the immune system's ability to respond to new infections and coordinate effective immune responses.[20]

2.3 Innate Immune Dysregulation and Inflammaging

Ageing impacts the innate immune system significantly, contributing to a state known as immunosenescence. Innate immune cells, including macrophages, neutrophils, natural killer (NK) cells, and phagocytes, exhibit functional declines with age. Macrophages exhibit reduced phagocytic activity and impaired cytokine production, thereby affecting their ability to initiate and regulate immune responses.[21] They also exhibit decreased expression of pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), leading to impaired pathogen recognition and response.[22] Neutrophils mediate the immediate host response to bacterial and fungal infections, which are largely responsible for the higher rates of mortality and morbidity in the elderly population. Neutrophils experience diminished chemotaxis, phagocytosis, and reactive oxygen species (ROS) production, hampering their capacity to combat infections. [23] NK cells display reduced cytotoxicity and altered cytokine secretion profiles, weakening their effectiveness in controlling viral infections and tumours.[6] Additionally, the increased production of pro-inflammatory cytokines by senescent cells, including macrophages and other phagocytes, leads to a chronic low-grade inflammatory state termed "inflammaging," which is linked to various age-related diseases.[24] These changes collectively impair the innate immune system's ability to respond to pathogens, contributing to increased susceptibility to infections and a decreased response to vaccinations in the elderly

Altered Cytokine Production: Ageing affects cytokine production, leading to a state of chronic low-grade inflammation known as "inflammaging." This is characterised by elevated

levels of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) (Figure 2). Inflammaging is linked to a variety of age-related diseases, including cardiovascular disease and neurodegenerative disorders. [52, 53] The reshaping of cytokine expression pattern with a progressive tendency toward a pro-inflammatory phenotype has been called "inflammaging" and is found associated with age-related diseases. (Figure 2).

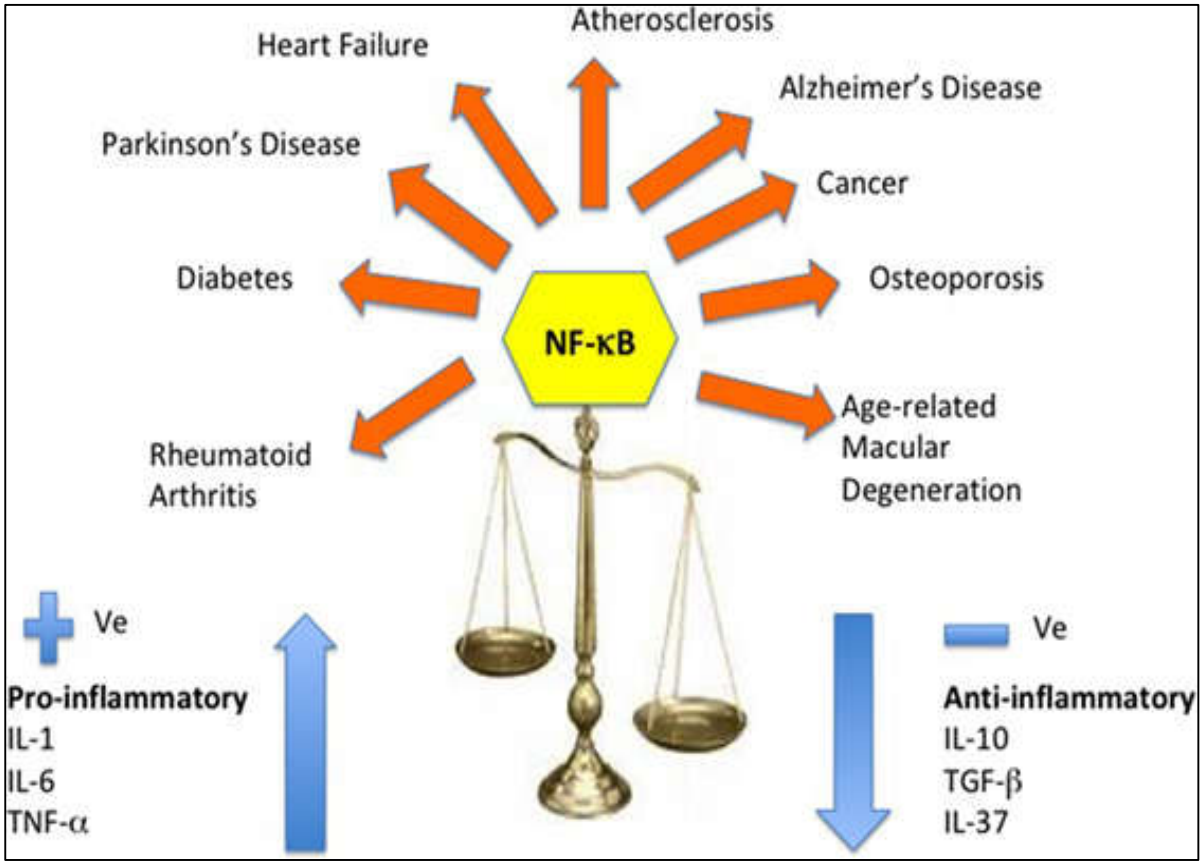

Figure 2. Several molecular pathways have been identified that trigger the inflammasome and stimulate the NF-κB and the IL-1β-mediated inflammatory cascade of cytokines.[25] (Source: https://doi.org/10.3389/fimmu.2018.00586).

Natural Killer (NK) Cells: Natural killer cells are essential for early defence against viral infections and tumour surveillance. While NK cells themselves are short-lived (around two weeks), human NK cells exhibit telomere shortening and a decrease in telomerase activity with age.[58] Also, the number and cytotoxic activity of NK cells decline, impairing their ability to eliminate infected and malignant cells. Natural killer (NK) cells, critical for targeting virally infected cells and tumours, undergo significant changes with ageing, contributing to immunosenescence. Ageing reduces NK cell cytotoxicity, partly due to decreased expression of activating receptors like NKG2D, and alters cytokine production, with decreased interferon-

gamma (IFN-γ) and increased pro-inflammatory cytokines, contributing to chronic inflammation. [6, 26] The proportion of less mature CD56 bright NK cells increases while the more cytotoxic CD56 dim NK cells decrease.[27] Additionally, older NK cells exhibit impaired proliferation and expansion in response to cytokine stimulation and increased expression of inhibitory receptors such as killer cell immunoglobulin-like receptors (KIRs), further reducing their effectiveness [28, 29] These changes collectively weaken the innate immune response in the elderly, increasing susceptibility to infections and reducing tumour control. he aged environment might lack the stimulating factors necessary to achieve maximal NK function. With age, the levels of IL-2 and IL-15, vital cytokines for NK cell development and survival, decline, which may contribute to the decline in NK cell surveillance. In parallel, the levels of inflammatory cytokines, such as IL-6 and GDF15, increase with age, contributing to the aged inflammatory microenvironment. Treatment of NK cells in culture with interleukins 2, 12, or 15 (IL-2, IL-12, IL-15) and interferon-α (IFN-α) can increase their cytotoxicity towards cancer cells and even toward cancer lines that are generally resistant to NK cell killing. [59]

3. Clinical Implications

Age-related changes in the immune system, particularly in T-cells, B-cells, macrophages, and natural killer (NK) cells, lead to several clinical consequences, including heightened vulnerability to infectious diseases, an increased risk of cancer, and the emergence of autoimmune conditions. The decline in naive T-cell production and the accumulation of dysfunctional memory T-cells reduce the ability to respond to new infections, making older adults more susceptible to diseases such as influenza and COVID-19. One of the most striking features is the decline in naïve T-cell production, primarily due to thymic involution that begins early in adulthood. As the thymus shrinks, the repertoire of newly generated T-cells diminishes, leading to reduced diversity in the T-cell receptor pool. At the same time, there is an accumulation of memory and senescent T-cells, many of which are functionally exhausted and produce pro-inflammatory cytokines. This imbalance weakens the ability to mount responses to novel pathogens and vaccines, explaining why older adults are disproportionately vulnerable to infections such as influenza, COVID-19, respiratory syncytial virus (RSV), and pneumonia.[1, 2]

Similarly, B-cell function declines with age. There is a reduction in the generation of naïve B-cells from the bone marrow, alongside impaired class-switch recombination and somatic hypermutation in germinal cells. As a result, antibody responses in older adults are often weaker, less specific, and shorter-lived. This contributes not only to increased infection risk

but also to reduced vaccine efficacy, necessitating modified vaccination strategies such as higher-dose or adjuvanted formulations for the elderly.[4]

The innate immune system also undergoes profound remodelling. Macrophages display diminished phagocytic activity, reduced antigen presentation, and impaired pathogen clearance.[22] Meanwhile, natural killer (NK) cells, which play a crucial role in antiviral defence and tumour surveillance, show changes in both number and function—some subsets expand while others decline, but overall cytotoxic efficiency is compromised. These shifts reduce the capacity to eliminate virus-infected cells and malignant cells, thereby increasing the risk of cancer development in older populations.

Paradoxically, immunosenescence is accompanied by inflammaging—a state of chronic, low-grade inflammation characterized by elevated circulating levels of pro-inflammatory mediators such as IL-6, TNF-α, and CRP. This persistent inflammatory milieu not only accelerates tissue damage and age-related pathologies but also contributes to the emergence of autoimmune conditions, where self-tolerance breaks down, and the immune system begins to target host tissues.

Collectively, these alterations create a clinical picture where older adults face heightened susceptibility to infections, reduced vaccine responsiveness, elevated cancer risk, and a predisposition to autoimmune and chronic inflammatory disorders. Understanding these changes is critical for designing tailored immunotherapies, vaccination strategies, and lifestyle interventions—such as regular physical activity, optimal nutrition, and infection control measures—to help mitigate the impact of immunosenescence on ageing populations.

For instance, the impaired adaptive immune response contributes to higher mortality and morbidity rates from these infections in the elderly.[2,7] Similarly, reduced NK cell cytotoxicity and altered cytokine production weaken the immune system's ability to control viral infections and tumours, increasing the risk of oncogenesis.[6] Furthermore, ageing immune cells often produce pro-inflammatory cytokines, leading to a chronic inflammatory state known as "inflammaging," which can drive the development of age-related autoimmune conditions such as rheumatoid arthritis and systemic lupus erythematosus.[24] Collectively, these immune changes underline the need for targeted medical interventions to improve immune function in the elderly.

4. 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.

4.1 Tailored Vaccination Protocols

High-Dose Vaccines: High-dose influenza vaccines have shown increased efficacy in older adults by stimulating a stronger immune response compared to standard-dose vaccines.[30] Additionally, the COVID-19 pandemic exposed older adults' vulnerability to respiratory infections and marked the first widespread use of mRNA vaccines. The two leading mRNA COVID-19 vaccines, based on nucleoside-modified mRNA encoding an optimised SARS-CoV-2 spike protein, elicited robust T- and B-cell responses in older adults, though weaker than in younger adults, with frail individuals showing the lowest responsiveness. [51]

Adjuvanted Vaccines: Vaccines with adjuvants, such as the MF59-adjuvanted influenza vaccine, enhance the immune response by providing stronger and longer-lasting immunity.[31]

Booster Doses: Regular booster doses can help maintain immunity, particularly for vaccines like Tdap (tetanus, diphtheria, and pertussis) and pneumococcal vaccines.[32]

Immunomodulatory Therapies: In the context of age-related immune system changes, immunomodulatory therapy focuses on counteracting the effects of immunosenescence—the gradual decline in immune function associated with ageing. Novel immune-modulatory theories addressing age-related changes are listed in the table below (Table 1). These therapies aim to restore or enhance immune function in older adults. The outlines innovative immune-modulatory strategies proposed to counteract age-related immune decline. These include epigenetic programming (altering DNA methylation and histone modifications to rejuvenate immune cells), metabolic reprogramming (using caloric restriction mimetics and metformin to boost immune metabolism), and mitochondrial enhancement (stimulating mitochondrial biogenesis and applying mitochondria-targeted antioxidants to reduce oxidative stress). It further highlights SASP modulation (inhibiting or modifying harmful secretions from senescent cells), autophagy enhancement (inducing autophagy or using rapamycin to clear damaged components), and artificial thymic organoids (developing lab-engineered thymic tissue to restore T-cell development). Finally, redox modulation through redox-active compounds and Nrf2 activators is proposed to strengthen antioxidant defenses and reduce inflammation. Together, these approaches represent a comprehensive roadmap for rejuvenating immune function and mitigating the effects of immunosenescence.[52]

Table 1. Novel immune-modulatory theories in addressing age-related changes in the immune system:

S.No.	Therapeutic Approach	Mechanism/ Description	References No.
1.	**Epigenetic Programming**	**DNA Methylation:** Altering DNA methylation patterns to rejuvenate immune cells.	33
		Histone Modification: Targeting histone modifications to restore youthful gene expression profiles in immune cells.	34
2.	**Metabolic Reprogramming**	**Caloric Restriction Mimetics**: Using compounds that mimic the effects of caloric restriction to enhance immune function.	35
		Metformin: Investigating the use of metformin to improve immune cell metabolism and function.	36
3.	**Mitochondrial Enhancement**	**Mitochondrial Biogenesis**: Promoting the formation of new mitochondria to improve the energy supply of immune cells.	37
		Mitochondrial Targeted Antioxidants: Reducing oxidative stress in mitochondria to enhance immune cell function.	38
4.	**Senescence-Associated Secretory Phenotype (SASP) Modulation**	**SASP Inhibitors**: Using drugs to inhibit the pro-inflammatory secretions of senescent cells.	39
		Senomorphics: Modifying the phenotype of senescent cells to reduce their harmful effects	40
5.	**Autophagy Enhancement**	**Autophagy Inducers**: Promoting the process of autophagy to clear damaged cellular components and improve immune cell function.	41
		Rapamycin: Exploring the use of rapamycin and its analogs to enhance autophagy and immune function.	42

6.	**Artificial Thymic Organoids**	**Thymic Organoids**: Developing artificial thymic organoids to support T-cell development and rejuvenation.	43
		Bioengineered Thymus: Creating bioengineered thymus tissue for transplantation and immune system rejuvenation.	44
7.	**Redox Modulation**:	**Redox-Active Compounds**: Using compounds that modulate the redox state of immune cells to enhance their function.	45
		Nrf2 Activators: Activating the Nrf2 pathway to boost antioxidant defenses and reduce inflammation.	46

5. Lifestyle Interventions

Exercise: Regular physical activity has been shown to improve immune function and reduce the incidence of infections.[47] Physical fitness is determined by several measurable health-related phenotypes, including mainly cardiorespiratory fitness and muscle function. Physical exercise has a profound effect on the expression of a substantial proportion of our genome, which has evolved to optimise aerobic metabolism in an environment of food scarcity. Thus, physical inactivity is becoming a major public health problem worldwide. Exercise certainly cannot reverse the ageing process, but it does attenuate many of its deleterious systemic and cellular effects.[62]

Nutrition: Nutrition and the intake of specific bioactive dietary components interact closely with immune function and inflammatory status, thereby establishing a strong link with the hallmarks of immunosenescence. The high prevalence of longevity and the low incidence of cardiovascular diseases observed in many Mediterranean countries highlight the importance of a diet rich in fruits, vegetables, whole grains, legumes, and olive oil, considered one of the key anti-ageing components of this region. [60] A balanced diet rich in antioxidants, vitamins (like vitamins D and E), and minerals (such as zinc and selenium) can support immune health.[48, 54]Equally significant is the reduced intake of animal proteins, particularly red and processed meats. The beneficial effects of this dietary pattern are attributed to its ability to attenuate inflammation and oxidative stress, while also supporting microbiota eubiosis, which collectively contribute to an enhanced immune response in these populations. [60]

Stress Management: Psychological stress is recognized as a significant risk factor for a wide range of diseases. A common underlying mechanism in these conditions is cellular senescence, which leads to functional impairments and is linked to cancer as well as cardiovascular, neurodegenerative, and autoimmune disorders. While such pathologies are typically associated with overall ageing, persistent and severe stress can precipitate their onset much earlier in life.[61] Chronic stress negatively impacts immune function, so practices like mindfulness, meditation, and other stress-reducing activities can benefit overall immunity.[49]

Adequate Sleep: Sleep serves as a restorative process that enables both the brain and body to recover from the demands of wakefulness. Beyond replenishing energy and enhancing cognitive focus, it is also proposed to facilitate cellular repair. According to this model, sleep is fundamental to maintaining biological health and reducing disease vulnerability. It aligns with existing paradigms that identify ageing biology as a central factor in the development of age-related conditions, including cardiovascular disease, diabetes, osteoporosis, and dementia. Ensuring sufficient and quality sleep is crucial for maintaining immune function, as sleep deprivation can impair immune responses [50]

Implementing these strategies can help mitigate the effects of immunosenescence, reduce susceptibility to infections, and improve the quality of life for the elderly.

6. Outcome

The outcome of this review reveals that immunosenescence is a multifaceted remodeling of both innate and adaptive immunity, leading to increased susceptibility to infections, cancer, and autoimmune diseases in the elderly.[55] A key consequence is reduced vaccine responsiveness, underscoring the importance of tailored strategies such as high-dose, adjuvanted, and mRNA-based vaccines to improve protection.[51] The chronic inflammatory state of “inflammaging” further accelerates age-related comorbidities, while emerging immunomodulatory approaches—including senolytics, metabolic reprogramming, and thymic bioengineering—show promise in reversing immune decline.[52, 53] Additionally, lifestyle-based interventions such as antioxidant-rich diets, regular exercise, stress reduction, and adequate sleep have been shown to buffer immune ageing and enhance resilience. Collectively, the outcome underscores that an integrated strategy, combining vaccination, therapeutics, and lifestyle modifications, is essential to extend healthspan and mitigate the burden of ageing-related immune dysfunction.

6.1 Relevance of the study

This study is highly relevant as it addresses the critical issue of immunosenescence, a central factor influencing health outcomes in ageing populations. With global life expectancy increasing, age-related decline in immune function has emerged as a major public health concern, contributing to higher susceptibility to infections, reduced vaccine responsiveness, increased cancer risk, and autoimmune disorders. By linking mechanistic insights such as thymic involution, T- and B-cell dysfunction, and inflammaging with their clinical implications, the study bridges basic immunology with applied healthcare. Furthermore, the discussion of tailored vaccination approaches, novel immunomodulatory therapies, and lifestyle-based interventions provides actionable strategies for improving immune resilience in older adults. This integrative perspective not only supports the development of age-specific vaccines and therapeutic innovations but also informs preventive healthcare practices and policy planning. Therefore, the study makes a significant contribution to advancing research, clinical practice, and public health initiatives focused on promoting healthy ageing and reducing the burden of age-associated diseases.

7. 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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9. Author's Contribution

DK: Conceptualisation, Writing- Original Draft, Visualisation.

10. Conflict of Interest

No conflict of interest

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