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Review

Endocrino-Immuno-Senescence and Its Correlation with Age-Related Diseases: Molecular Insights into Immunomodulatory Strategies for Healthy Aging

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ABSTRACT: Regulation of the endocrine and immune system is pivotal for bodily homeostasis and healthy physiology, and these processes deteriorate as life progresses from adulthood to senescence. Aging, progressively weakening the structural and functional efficacies of the hypothalamic-pituitary-thyroid-adrenal-gonadal autoregulating axis, results in endocrino-immuno-senescence (EIS) that modulates a variety of complications and diseases. Both endocrine and immune responses are compromised during aging, along with impaired tissue regeneration, weakened pathogen detection, and decreased immune surveillance, and these events increase the susceptibility to infection, autoimmunity, cancers, and chronic disorders. Nonetheless, while immunosenescence modulates systemic inflammation and overall host defense, inflammaging accelerates tissue deterioration and intensifies diverse pathologies. Dysregulation of hormonal, genetic, and epigenetic machineries dampens the immune system, elevates pro-inflammatory activity, and fails to defend an organism against foreign pathogens, representing a link between cellular dysfunction and EIS. To mitigate these events, immunomodulation is an important therapeutic strategy that helps renew endocrine and immune dysregulation and simultaneously diminish age health disparities. Moreover, preservation of hormonal stability, involving immune response, emerges as a central determinant and could serve as a preventive medicine for the health and well-being of aged populations. This review provides a comprehensive understanding of the mechanisms by which EIS is coordinately associated with a variety of pathological processes and delineates new insights into immunomodulatory strategies ameliorating age-related diseases for healthy aging and quality living.

Keywords: Endocrine and immune dysregulation, Immunosenescence, Inflammaging, Age-related diseases, Immunomodulation, Healthy aging

1. Introduction

Hormone-immune interactions are intricately regulated in numerous biological processes. Specifically, whereas endocrine alterations impact immune responses, chronic activation can perturb hormone profiles, resulting in various diseases [1]. Hormonal equilibrium has widespread consequences on metabolism, growth, stress response, reproduction, and immune regulation [2, 3]. In contrast, age-associated hormonal imbalance contributes to various diseases and certain cancers by impacting the immune system. Hormone deficiencies, especially estrogen and androgen levels, influence cell differentiation, leading to enhanced humoral immunity and a greater prevalence of autoimmune diseases in females compared to males. Specific endocrinological

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transitions, such as puberty, pregnancy, and menopause, alter both innate and adaptive immune activities through modulation of cytokines and T-cell polarization [4]. Overall, hormonal inequality includes, but is not limited to, inefficient hypothalamic-pituitary-thyroidal-adrenal-gonadal (HPTAG) axes, impaired memory and cognitive function, sexual dysfunction and depression, increased risk of cardiovascular diseases (CVDs), and certain cancers [2, 3, 5-7].

The occurrence of hormone deficiencies, affecting the functions of a multitude of organs, is the major cause of human senescence [8]. Aging, involving impaired physiological activities, represents a major global challenge with profound social, economic, and health implications [9, 10]. A growing urgency is to develop strategies that not only extend the lifespan but also enhance the quality of life in geriatric populations. A central biological process underlying aging is cellular senescence, which occurs in response to cumulative stress, DNA damage, telomere attrition, and a host of other events [11, 12]. Senescent cells secrete pro-inflammatory cytokines, chemokines, growth factors, and proteases, and are referred to as senescence-associated secretory phenotype (SASP) [13]. Persistent SASP contributes to a chronic, low-grade inflammatory environment that disrupts bodily homeostasis and impairs regenerative capacity. This inflammatory burden plays a critical role in diminished immune surveillance, altered competence, reduced responsiveness to pathogens, and enhanced vulnerability to age-related diseases [14, 15]. Central to this process is the dysregulation of the endocrine system, which plays an important role in coordinating metabolic, immune, and cellular processes. Hormonal homeostasis orchestrates inter-organ communication and modulates energy balance, stress response, tissue maintenance, and repair processes. With aging, quantitative and qualitative declines in hormone profiles modulate endocrino-immuno-senescence (EIS) and contribute to a variety of pathologies [16, 17]. EIS refers to the bidirectional dysregulation between endocrine and immune function, driven by a variety of events, including epigenetic drift, mitochondrial dysfunction, and chronic inflammation, modulating the development of age-related diseases. This conceptual framework, involving endocrine aging, immunosenescence, inflammaging, and cellular senescence, affects the disease onset, severity, and recovery trajectories.

An overwhelming amount of evidence indicates that immunomodulatory approaches, including vitamins, diet and nutrition, hormonal, pharmacological, and stress management, have been reported to alleviate both endocrine and immune outcomes during aging [18-20]. Along these lines, regular physical activity lowers circulating cortisol levels and improves sleep quality, both of which support hormonal stability [21, 22]. Macro- and micro-elements influence hormone production and immune regulation. Whereas healthy diets support gut-microbiota diversity for restoring EIS, dysbiosis is linked with immune dysregulation and hormone imbalance [23]. The mechanistic link between stress hormones and endocrine dysfunction has been reported with dampened immune responses [24, 25]. Hormonal disparities are intertwined with disease processes through complex endocrine-immune crosstalk. Overall, nutrition, stress management, sleep optimization, and healthy lifestyles alleviate not only immunomodulation but also endocrine-immune stability, and these interventions can mitigate disease risk and promote healthy aging.

2. Hormonal Diversity in Physiology and Pathophysiology

The endocrine system consists of a coordinated network of ductless glands and specialized tissues that synthesize and release hormones into the bloodstream to regulate essential physiological functions [26, 27]. Hormones play a vital role throughout the lifespan, which interact with one another through stimulatory, inhibitory, or synergistic mechanisms [28]. A central feature of endocrine regulation is the hierarchical control exerted by the HPTAG axis (Fig. 1). The hypothalamus integrates neuronal, metabolic, and environmental cues [18, 29]. Pituitary hormones act on the thyroid, adrenal cortex, and gonads to stimulate the production of downstream signaling that governs a variety of processes, including metabolism, stress, and reproduction, which are impacted by tightly regulated feedback loops. The concentration of the hormones from the target glands rises to appropriate levels, which signals back to the hypothalamus and pituitary to suppress further stimulation, preventing and maintaining systemic balance [30].

A major neuroendocrine axis is the hypothalamic–pituitary–gonadal (HPG) system that regulates endocrine homeostasis through hierarchical signaling [29, 30]. The HPG axis governs sex steroid biosynthesis and reproductive function via pulsatile gonadotropin-releasing hormone (GnRH), which helps secrete luteinizing hormone (LH) and follicle-stimulating hormone, and these are regulated by circadian, metabolic, and developmental cues [31, 32]. By integrating signals from circulating sex steroids, these neuropeptides fine-tune gonadotropin release, ensuring appropriate reproductive hormone dynamics and maintaining functional stability of the HPG axis in both sexes. Steroid hormone biosynthesis initiates on the transport of cholesterol from the outer to the inner mitochondrial membrane, a process that is regulated by the steroidogenic

acute regulatory (StAR) protein [3, 33]. With aging, the HPTAG axis shows diminished activity and peripheral glands become less responsive, resulting in dampened hormone synthesis, reduced receptor sensitivity, and altered metabolism, all of which modulate EIS [34]. A hallmark of endocrine-immune aging is the disruption of circadian and pulsatile secretion patterns, including cortisol and sex steroids [17, 35]. Studies have indicated that chronic low-grade inflammation impairs neuroendocrine function, creating bidirectional feedback events between immune and endocrine systems [36], resulting in age-related declines in peripheral hormones [37]. Chronic activation of the HPA axis exacerbates stress and metabolic conditions and reduces physiological resilience in older adults [17, 38]. Besides, thyroid disorders, involving elevated thyroid-stimulating hormone (TSH) with stable T4, are more prevalent in women. Notably, both increased TSH and hypothyroid states are associated with cognitive decline, fracture risk, cardiovascular complications, and higher mortality [17, 30, 39]. Reduced sex steroid signaling with increased GnRH, LH, and activin disrupts systemic and neuronal homeostasis, contributing to cognitive, reproductive, and metabolic disorders [40]. Therefore, the HPTAG autoregulatory system is tightly linked to immune aging (Fig. 1). Declining endocrine function, reflected by circadian rhythms, impaired feedback control, and reduced cellular activities, promotes chronic low-grade inflammation and immune deficiency [41-43].

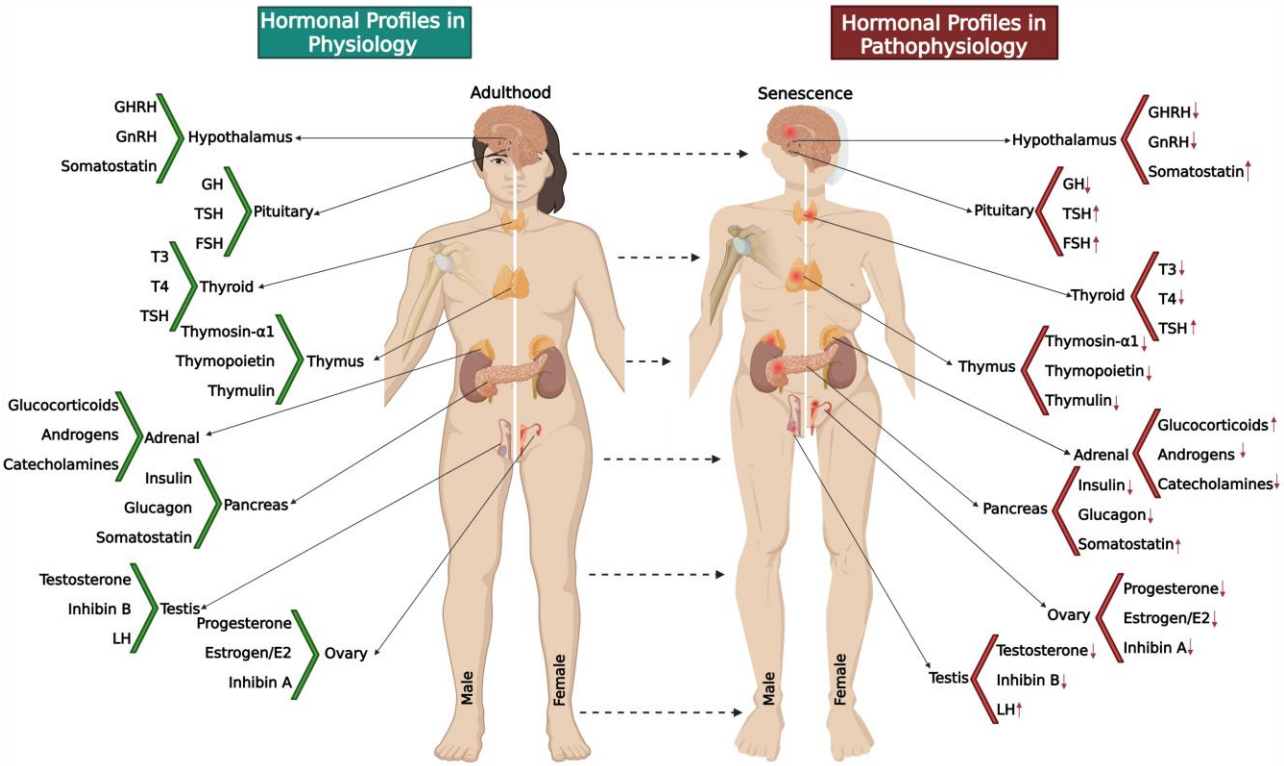

Figure 1. Hormonal profiles under physiological and pathophysiological conditions in women and men. A schematic representation illustrates levels of various hormones across the HPTAG autoregulatory system pertaining to adulthood and senescence. Specifically, hormonal homeostasis is maintained for upholding diverse physiological activities during adulthood (*left half*). In contrast, hormonal imbalance, affecting the structural and functional efficacies of a multitude of organs, is a common occurrence in human senescence (*right half*). The manifestations of hormone deficiencies, modulating immune function, influence a variety of health issues, ranging from reproduction to neurodegeneration to carcinogenesis. As a consequence, while appropriate hormone regulation sustains required physiological activities, disrupted hormone balance in aging, modulating immunosenescence, is vulnerable to age-related diseases in both women and men. Arrows indicate diverse hormone profiles during aging.

3. Sex-Specific Endocrine and Immune Mechanisms

There is a close correlation between the endocrine and immune systems, mediated by cytokines, cellular signaling, and receptor-effector coupling, which regulate metabolism, stress response, and host defense in both sexes [44, 45]. However, these processes deteriorate during aging, resulting in EIS, and are influenced by tissue remodeling. Endocrine-immune aging is differentially influenced by sex, a biological factor. Epidemiological, transcriptomic, and pathological evidence indicate that women and men differ not only in age-related disease prevalence, but also in the disease onset, progression, and clinical manifestation [46, 47]. Disruption of sex-specific

gonadal hormones in aging, involving immunosenescence, influences pathogen defense and chronic inflammation, and heightens individuals' susceptibility to autoimmune, metabolic, and neurodegenerative disorders, especially Alzheimer's disease (AD) [45, 46, 48, 49]. Specifically, late-onset sporadic AD preferentially affects more women than men and is impacted by a variety of factors and/or events, including occluded neurosteroidogenesis, mitochondrial dysfunction, and epigenetic dysregulation, in which EIS plays an indispensable role [45, 50, 51]. The functional decline of the HPTAG auto-regulatory system results in the progression of various age-related diseases in both sexes. Generally, women, compared with men, have stronger immune responses, along with higher CD4+ T-cell counts, antibody efficacies, and longer telomere lengths. Estrogens in women increase immunity by promoting antibody production, B-cell maturation, and T-cell activation, resulting in stronger vaccine responses [47, 52, 53]. Conversely, testosterone in men exhibits immunosuppressive properties due to decreased proliferation of T-cells, cytokines, and B-cell activity, leading to reduced susceptibility to autoimmune diseases. The life expectancy in women is higher than in men, which might make the former group more vulnerable than the latter to the progression of diseases, in which a sudden drop of estrogens at menopause and a gradual decrease in testosterone at andropause, respectively, with elevated LH and FSH levels, play permissible roles.

Senescence is typically associated with aging, modulates endocrine-immune signaling, and it occurs due to various events, including DNA damage, telomere shortening, and oncogenic signaling. Genomic instability and epigenetic drift, involving biological aging, are more pronounced in males than in females, which contribute to repair mechanisms being less efficient [46, 49]. Sex-specific hormonal differences, especially estrogen and testosterone levels in women and men, respectively, and their depletion, modulating EIS, have diverse consequences in age-associated pathologies, which are also impacted by disruption of metabolism, gut microbiota, and autophagy [47, 54, 55]. Sex is a critical biological variable for evaluating EIS because gonadal hormones decline at different rates in women and men, along with immune responses, disease prevalence, and severity. Considering the involvement of sex-specific disease differences and mechanistic underpinnings, clinical trials should target an equal number of males and females to yield a conclusive outcome. Moreover, an overwhelming amount of evidence indicates that sex-specific interactions between endocrine and immune aging play key roles in shaping health outcomes in geriatric populations; thus, there are considerations for therapeutic interventions for the reversal of EIS, vaccine efficacy, and healthy aging [52, 56, 57].

4. Age-Associated Disruption of Cellular Senescence and Immunity

Aging is an inevitable heterogeneous phenomenon involving whole-body tissue remodeling that impacts EIS. Cellular senescence is a central mechanism, and it refers to a stable and irreversible arrest of diverse relevant processes, including metabolism and chromatin architecture [58, 59]. Senescence is initiated by a variety of intrinsic and extrinsic stressors, including telomere shortening, double-strand DNA breaks, oxidative stress, mitochondrial dysfunction, epigenetic perturbations, inflammation, and metabolic dysregulation [60-62]. Cellular senescence participates in normal physiological processes such as tissue remodeling during development, wound healing, and fibrosis regulation. Senescent cells also exhibit disturbances in proteostasis and autophagy, and an increase in reactive oxygen species (ROS) [61, 63]. One of the most important consequences of EIS is the implementation of a pro-inflammatory and tissue-modifying SASP, which encompasses a wide array of secreted factors, including cytokines, chemokines, and extracellular DNA fragments [64-66]. These factors exert autocrine, paracrine, and endocrine influences, altering the microenvironment, recruiting immune cells, affecting stem and progenitor cell behavior, and influencing systemic inflammation [65, 67]. Chronic accumulation of senescent cells contributes to organismal aging that involves impaired tissue regeneration and intercellular communication, and contributes to CVDs, neurodegeneration, and compromised immune responses [15, 63, 68, 69]. Because of its complex and context-dependent effects, senescence has been proposed as an example of evolutionary antagonistic pleiotropy, which is beneficial early in life for tumor suppression and tissue remodeling, but detrimental later due to accumulation of senescent cells [61, 62]. Regulation of immune responses during adulthood and senescence has been illustrated in Figure 2.

4.1. T- and B-cells senescence

T-cells undergo profound changes with aging and EIS, which are consistent with the acquisition of senescent features. Studies have reported that T-cell senescence is characterized by stable cell-cycle arrest, altered phenotype, and adoption of a pro-inflammatory secretory profile [15, 63, 70]. In aged individuals, thymic involution may result in a dramatic reduction in the output of naïve T-cells, narrowing T-cell receptor (TCR) diversity and impairing antigenic responsiveness [15, 63]. Senescent T-

cells exhibit diminished proliferative capacity in response to antigen or mitogenic stimulation, resulting in cytotoxic activity, immune function, and vaccine efficacy [63, 70]. Chronic antigenic stimulation, such as persistent viral infections or low-grade inflammation, can accelerate T-cell senescence, compounding the loss of naïve T-cells and function [70], with implications for age-related decline in adaptive immunity.

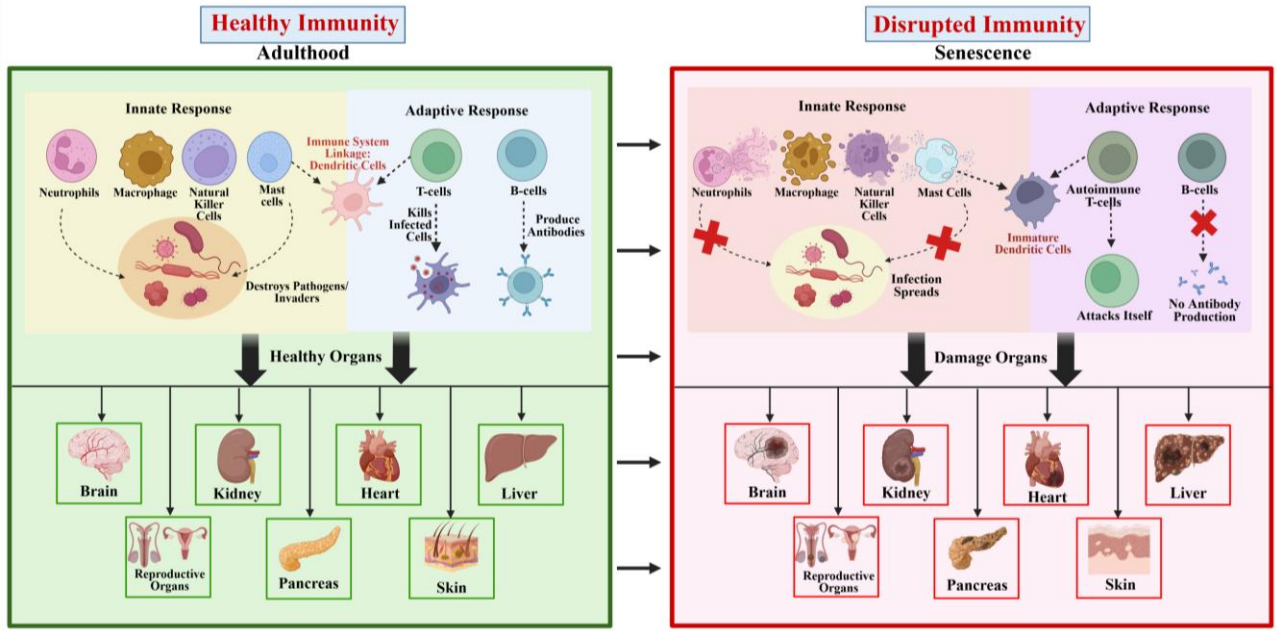

Figure 2. Age-associated changes in innate and adaptive immunity and their impact on health and diseases. A model depicts coordinated immune responses during adulthood (*panel A*). Innate immune cells, including neutrophils, macrophages, NK cells, and mast cells, effectively destroy pathogens, while dendritic cells bridge the innate and adaptive responses, activating T-cells to kill infected B-cells for producing antibodies. These events preserve the health of vital organs, including brain, kidneys, heart, liver, reproductive organs, pancreas, and skin. In contrast, immune competence is markedly disrupted during senescence (*panel B*), in which innate immune surveillance fails for infection to spread, while immature dendritic cells drive autoreactive T-cell responses and impair antibody production. This state of immune dysfunction culminates in organ damage across multiple tissues. Alterations of cumulative immune responses, involving healthy to disrupted immunity across the life span, are associated with physiological and pathophysiological processes, respectively.

B-cells show age-associated alterations in number, phenotype, and function, participating in the senescence mechanism [15, 70]. Specifically, the production of new naïve B-cells declines, limiting the ability to respond to antigens. Accumulation of B-cells affects lifelong antigen exposure and homeostatic shifts and exhibits impaired class-switch recombination and antibody affinity [15, 63]. Disruption of B-cells may also downregulate surface receptors crucial for reduced CD40 activation (9). The diminished B-cell function contributes to increased susceptibility to infectious diseases, reduced vaccine-mediated protection, and impaired immune surveillance. B-cell senescence involves pathways that alter chromatin regulation and SASP-like activity. Even so, the dynamics of B-cell subset changes remain less well-characterized than those of fibroblasts and T-cells, which are associated with senescence, differentiation, clonal selection, and survival [15, 70].

4.2. Other immune cell lineages: leukocytes, monocytes, macrophages, lymphocytes, eosinophils, and platelets

Besides T- and B-cells, EIS is impacted by other immune cell lineages, including monocytes, macrophages, lymphocytes, eosinophils, and basophils. Emerging evidence suggests that senescence in myeloid cells, particularly macrophages, can contribute to age-associated immune dysfunction, inflammation, and tissue pathology [15, 59, 71]. Monocytes and macrophages are vulnerable with age, and under persistent inflammatory stimuli, they can adopt a senescent phenotype characterized by growth arrest, altered metabolism, and a pro-inflammatory secretory profile. Senescent macrophages have been implicated in adaptive immune dysfunction, impaired tissue repair and metabolism, increased fibrosis, and chronic inflammation, promoting age-related diseases [59]. Other leukocytes, such as innate lymphoid and natural killer (NK) cells, may also

experience functional decline during aging, even though the occurrence of senescence in these immune-cell subsets is still unclear. Evidence suggests that chronic activation or stress may drive senescent-like differentiation, but the distinction remains ambiguous [15, 70]. Current understanding suggests that EIS is not simply a loss of competence but an active process of tissue remodeling that alters intercellular communication, degrades homeostasis, and propagates chronic inflammation [15, 69, 71]. Therefore, removing senescent cells or modulating their secretory profile restores immune responses, reduces inflammation, and improves tissue repair [15, 59, 71].

Tumor immune evasion is a multidimensional and evolutionary selected process that often occurs with EIS, in which cancer cells escape through distinct mechanisms. Reciprocally, tumors downregulate antigenic capacity to cytotoxic $CD8^+$ T-cells and simultaneously exploit inhibitory checkpoint pathways, including PD-1/PD-L1, CTLA-4, and TGF-β, to actively deactivate infiltrating immune effector cells [72]. Hypoxia-driven activity promotes metabolic reprogramming and recruits myeloid-derived suppressor cells and M2-polarized macrophages, establishing a profound immunosuppression [72-74]. Chronic antigen exposure further drives $CD8^+$ T-cell exhaustion, a state that is reinforced by mitochondrial dysfunction and epigenetic silencing [75]. Notably, cancer cells can directly transfer mutant mitochondria to tumor-infiltrating lymphocytes, evading mitophagy and inducing T-cell dysfunction through homoplasmic replacement [72]. Immunogenic subclones, evolving due to mutations or genetic alterations, are selectively eliminated by antitumor T-cell responses, while resistant clones persist and expand, generating intra-tumoral heterogeneity that correlates with poor prognosis and blockade resistance [76]. Tumor–host interactions, altering endocrine-immune signaling and encompassing antigen camouflage, immune coercion, and cyto-protection, render tumor immune evasion a layered, redundant, and therapeutically challenging process.

5. Aging and Dysregulation of the Immune System

Disruption of the immune system is intertwined with endocrine dysfunction during the process of aging, which gives rise to an array of complications, including increased susceptibility to cancer, neurodegenerative diseases, and infections. A key network of regulated processes that protects an organism from viruses, bacteria, and other pathogens involves two cooperative events, called the innate immune system and the adaptive immune system [77]. Whereas the former relies upon the physical features and gene expression of an organism and provides defense against pathogens, the latter's protective influence involves antibody-based mechanisms [78].

5.1. Innate immune dysregulation

Innate immunity governs early pathogen sensing, initiation of anti-viral and anti-bacterial programs, and orchestration of leukocyte recruitment. With age, innate immune signaling often displays a paradoxical phenotype, involving elevated inflammation with impaired performance within the context of an acute microbial challenge [79, 80]. The increase in danger-associated molecular patterns evolves due to cumulative cellular stress, impaired proteostasis, and mitochondrial dysfunction. When immune clearance of senescent cells is incomplete due to impaired cytotoxicity and altered chemotaxis, SASP can reprogram macrophages, disrupt stromal niches, and cause chronic inflammation [81, 82]. Overall, age-dependent endocrine-immune dysfunction is impacted by cellular senescence, inflammation, and genomic instability (Fig. 3).

5.2. Inflammasomes

A link between age-related cellular stress and chronic inflammation has been implicated with inflammasomes [83, 84]. The NLR family, pyrin domain-containing 3 (NLRP3) mediated inflammasome, is activated by diverse EIS mediated stress signals, including mitochondrial dysfunction, ion fluxes, and ROS, and it increases production of mature interleukins, 1β (IL-1β) and IL-18. It has been demonstrated that the canonical NLRP3 activity can link systemic low-grade inflammation to functional decline, supporting a causal role for inflammasome-mediated cytokine maturation [85]. Metabolic intermediates can activate inflammasomes, in which ketone metabolite β-hydroxybutyrate inhibits NLRP3, underscoring the tight coupling of innate inflammation to nutrient sensing [86]. Hematopoiesis is an upstream driver that shapes innate immunity by altering the production and function of myeloid cells [87-89]. Hematopoietic stem cells accumulate DNA damage and epigenetic alterations over time, which can preserve innate cell numbers by changing inflammation and reducing lymphoid replenishment [90, 91]. The well-known markers of hematopoietic stem cells include, but are not limited to, ABCG2, CD34, CD38, and CD90. Besides, hematopoietic clones become more prevalent with age-associated EIS, reflecting the expansion of somatic mutations that can skew inflammatory programs [92]. Studies have shown that TET2 mutations affect immune function, in which clonal hematopoiesis can accelerate CVDs, blood cancers, and autoimmune diseases through IL-1β–linked inflammatory signaling,

and these events are impacted by disrupted endocrine signaling [93, 94].

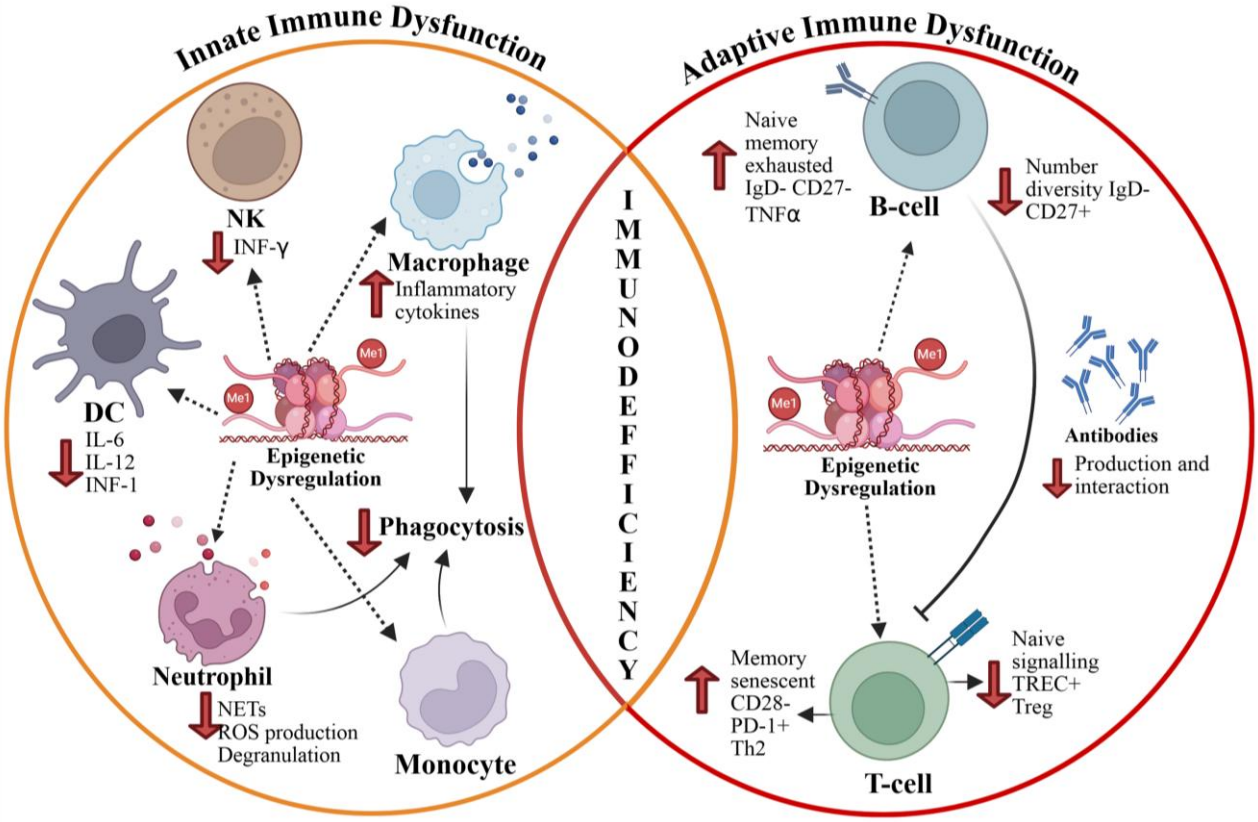

Figure 3. Involvement of diverse signaling in innate and adaptive immune dysfunction. A schematic model shows cellular alterations associated with immunodeficiency and its resulting consequences. Epigenetic dysregulation modulates immune responses, contributing to age-associated diseases. The *left circle* depicts innate immune alterations that include reduced NK cell activity with diminished IFN-γ production, impaired dendritic cell (DC) signaling associated with decreased IL-6, IL-12, and type I interferon, and compromised responses inflicted by reduced neutrophil extracellular trap (NET) formation, ROS generation, and degranulation. Aging macrophages exhibit heightened inflammatory cytokine production along with reduced phagocytic capacity. The *right circle* illustrates adaptive immune dysfunction, where B-cells display diminished antibody production and cellular interactions, reduced frequency and diversity of $IgD^{-}CD27^{+}$ memory subsets, and accumulation of senescent memory populations ($IgD^{-}CD27$-TNFα). T-cell alterations include reduced naïve T-cell signaling, expansion of memory and senescent phenotypes ($CD28^{-}PD\text{-}1^{+}Th2$), and dysregulated regulatory T-cell (Treg) function. Dysfunction of innate and adaptive immunity results in immunodeficiency (*middle*).

5.3. Neutrophils

Neutrophils exemplify how innate cell populations can be maintained while function becomes dysregulated [95, 96]. Deterioration of age-associated endocrine-immune signaling is associated with impaired neutrophil chemotaxis, which can delay pathogen containment and increase reliance on prolonged inflammation that damages host tissues [97]. Older individuals also exhibit diminished formation of neutrophil extracellular traps, which can reduce antimicrobial efficacy while altering the balance between pathogenic clearance and collateral tissue injury. Because neutrophils affect antigen load, tissue damage, and cytokine environments, these defects can blunt adaptive priming toward dysfunctional trajectories [98].

5.4. Monocytes and macrophages

Monocytes and macrophages play important roles in the appropriate functioning of the immune system because they integrate tissue-derived damage signals, microbial products, and metabolic cues to determine inflammatory output and resolution [79, 99]. Aging, involving EIS, can alter toll-like receptor (TLR) signaling and cytokine production by evolving a state in which basal inflammatory mediator release is increased with reduced antimicrobial functions [100]. Reduced efferocytosis contributes to persistence of cellular debris and secondary

necrosis, sustaining innate immune activation and reinforcing inflammation [79]. Dendritic cells are particularly relevant to aging because they bridge between innate and adaptive immune sensing. Age-associated reductions in TLR function in dendritic cell subsets have been shown to predict influenza vaccine response, linking innate immune defects with impaired outcomes [101]. Additionally, deterioration of type I interferon signaling can limit T-cell differentiation and weaken vaccination efficacy, in which targeted innate stimulation can partially restore these pathways in aged individuals [102, 103].

5.5. NK cells

NK cells occupy an innate-like lymphocyte niche critical for antiviral defense and tumor immunosurveillance [104]. Human NK cells are divided into two principal subsets based on surface marker expression: the CD56brightCD16^{-} and the CD56dimCD16^{+} [105]. The occurrence of an increase in CD56brightCD16^{-} and a decrease in CD56dimCD16^{+} cells balances away from immunoregulation toward cytotoxic phenotypes [106]. With age-related modulation of EIS, activating receptors decline while inhibitory KIRs increase, especially on CD56bright NK cells, leading to weaker tumor and antiviral responses, reduced degranulation, and impaired perforin release, possibly due to disrupted Ca^{2+}-dependent exocytosis [107, 108]. Studies have demonstrated that changes in NK cell phenotypes, receptor repertoire, cytotoxicity, and cytokine production vary by tissue and health conditions [109, 110]. Furthermore, a unique PD-1^{+} NK cell subset emerges with high CD57 and CD69 levels, indicating overactivation and terminal differentiation [111]. In the context of acute infection, elderly individuals exhibit increased expression of SLAMF7, TIM-3, CD96, NKG2A, and TIGIT on NK cell subsets, along with an activated and terminally differentiated surface phenotype with elevated CD69 and CD57 levels. Changes in markers of terminal differentiation, such as cluster of differentiation 57 (CD57) in NK- and T-cell subsets, reflect broader shifts in distributions and proliferative reserve in aging immune responses [112]. Because NK cells help regulate maturation of dendritic cells and participate in surveillance of stressed or senescent cells, their dysfunction can amplify both infection susceptibility and accumulation of senescence-associated inflammatory burden [109, 113].

5.6. Microbiome

Microbiomes shape endocrine-immune aging by controlling baseline exposure to microbial products and providing signals that tune innate recognition [114, 115]. Age-associated dysbiosis has been shown to promote increased intestinal permeability, systemic inflammation, and macrophage dysfunction, indicating a plausible route by which microbiome remodeling can drive EIS [116]. This gut-driven immune activation can chronically influence innate receptors, raise cytokines, and induce an inflammatory state in myeloid cell populations that do not improve pathogen-specific defenses. Trained immunity provides a conceptual framework for durable innate reprogramming across the lifespan [117]. It describes epigenetic and metabolic remodeling of innate immune and progenitor cells after infections, vaccines, or inflammatory exposures, producing altered responsiveness to diverse challenges. Therefore, interventions that reduce chronic inflammatory load, either by metabolic correction, reduction of senescent cells, or modulation of innate sensors, may improve resilience even when they do not directly target a pathogen [118]. Since innate immune aging is linked to nutrient-sensing and cellular-maintenance programs, age-dependent interventions have begun to target these upstream regulators to improve endocrine-immune function [119, 120]. Pharmacologic inhibition of the PI3/AKT/mTOR pathway has been reported to improve immune function, supporting the involvement of nutrient-sensing in reverse immune aging phenotypes (Fig. 3).

6. Adaptive Immune Dysfunction

Dysregulation of age-related adaptive immunity emerges from structural constraints on leukocyte proliferation, accumulated antigenic history, and progressive remodeling of lymphoid microenvironments that govern cell survival, trafficking, and memory formation [121]. A defining driver is thymic involution, which reduces export of naïve T-cells and limits the generation of TCR activity required for responses to pathogens and vaccines. Reduced TCR diversity increases the probability that a protective, high-affinity precursor for a new antigen is absent, which contributes to delayed, weaker, and more variable immune responses in older adults [122, 123].

6.1. Alterations of T- and B-cells

T-cell aging emphasizes shifting the balance of naïve and memory subsets and increases the prevalence of differentiated states with reduced proliferative function [121]. Senescent T-cells are identified by co-expression of CD28^{-}, CD57^{+}, and KLRG1^{+}, particularly within the Terminally Differentiated Effector Memory T-cells re-expressing CD45RA (TEMRA) subset, which accumulates CD8^{+} T-cells with age. CD28-negative T-cells have been implicated in age-associated decline of immune adaptive function by competing with homeostatic

cytokines [124]. Identification of senescence-like differentiation from T-cell exhaustion is a dysfunctional program driven by persistent antigen exposure in chronic infection and cancer [125, 126]. Besides, a conceptual analysis has debated whether senescence and exhaustion are intertwined to compromise immunity in aging, where chronic infection, cancer incidence, and inflammation are more common. Persistent viral infections strongly shape adaptive immune aging [127, 128]. For example, cytomegalovirus (CMV) acts as a chronic antigenic stressor linked to immunodeficiency. Such CMV-driven remodeling can reduce the space available for naïve precursors and may contribute to diminished responsiveness to vaccines and pathogens [128] (Fig. 3). Following primary infection, CMV establishes lifelong latency with periodic reactivation that drives effector-memory and TEMRA subsets [129, 130]. These inflammatory T-cells display $CD28^{-}CD27^{-}CD45RA^{+}$ senescent phenotypes with reduced lymph node, inhibitory receptor expression, and limited TCR repertoire diversity [131, 132]. TCR repertoire sequencing has demonstrated that CMV seropositivity reduces its overall diversity by ~33% compared with seronegative individuals. CMV seropositivity is a core component of the immune risk profile, a cluster of parameters including CD4:CD8 inversion, late-differentiated T-cells, and poor proliferative response [133, 134]. Nevertheless, the relationship between CMV and dampening immune response is not detrimental, as data from murine models suggest that long-term CMV infection can broaden the TCR repertoire mobilized against infections through cross-reactive mechanisms [135].

B-cell aging is a major determinant of reduced vaccine efficacy [136, 137]. Aging can alter B-cell subset composition, reduce class-switch recombination and somatic hypermutation, and impair the generation of high-affinity and long-lived plasma cells, leading to less potent antibody responses. Germinal center (GC) biology is particularly sensitive to aging because it requires orchestrated interactions among antigen-retaining follicular dendritic cells, T follicular helper (Tfh)-, and B-cells [138]. Moreover, impaired dendritic cell activation and type I interferon signaling can precede defective Tfh cell differentiation, linking to humoral insufficiency through GC disruption. Humoral immune aging is a system-level defect spanning innate instruction, impacting differentiation and follicular microenvironment function. Nevertheless, age-associated B-cells act as protective and pathogenic immune utility, suggesting they can contribute to rapid responses under certain conditions while also associating with autoimmunity-like phenotypes and inflammatory outputs [138, 139]. Studies of aging lymph nodes define the structural and functional changes that can limit effective immune priming, consistent with reduced vaccine responsiveness and adaptive kinetics in mice [140].

6.2. Epigenetic drift

The epigenetic machinery progressively deteriorates with age and influences EIS, affecting gene expression, cellular function, and tissue homeostasis [141]. These changes integrate cumulative exposure history that includes infections, inflammation, and metabolic state, which help explain why immune responsiveness can diverge substantially among individuals of the same chronological age. Regulatory circuits also remodel with aging, influencing tolerance and balance between protection and pathology [142, 143]. Epigenetic clocks, emerging as invaluable tools, specifically utilize methylation patterns at a set of CpG sites, in which balanced combinations provide a reliable measure of biological age [144, 145]. In addition, chromatin accessibility and nucleosome positioning are also recognized as epigenetic clocks. Since EIS is tightly connected with epigenetic dysregulation, the reprogramming of the latter extends lifespan by mitigating age-related diseases [146, 147]. In aging T-cells, chromatin remodeling drives terminal differentiation and loss of epigenetic plasticity, contributing to EIS and susceptibility to infections, cancer, and autoimmune diseases [148]. Hence, epigenetic drift promotes lineage bias and stem cell decline, fostering hematological malignancies, in which epigenetic reprogramming can serve as therapeutic targets [149]. Additionally, immune and epigenetic dysregulation, involving hypermethylation and histone deacetylation, has been linked to neurodegenerative diseases, where aberrant methylation sustains vascular inflammation, highlighting HDAC and DNMT inhibitors as potential targets for interventions [70, 150].

7. Genetic and Epigenetic Dysregulation and Their Association with EIS

Malfunction in the genetic and epigenetic machineries, involving cellular functions, plays an important role in EIS, a fundamental driver of organismal aging and health complications. Epigenetic alterations refer to heritable changes in phenotype that occur with DNA methylation, histone modifications, chromatin remodeling, and transcriptional regulation by non-coding RNAs [151]. Activation of DNA damage in response to these lesions initiates cell cycle arrest, and chromatin alterations promote SASP. Furthermore, genomic instability contributes to chromosomal aberrations that result in transcriptional repression [52]. Loss of nuclear envelope proteins such as lamin B1 disrupts structural integrity and

permits chromatin fragmentation [151]. Circulating cell-free mitochondrial DNA, lacking introns and efficient repair mechanisms, has emerged as an intercellular signal and it has been linked with EIS [152]. Cytoplasmic DNA is a potent driver of an inflammatory state occurring independently of infection and is implicated in chronic pathologies such as cardiovascular and neurodegenerative diseases. Studies have demonstrated that cytosolic DNA sensing can activate the AKT/mTOR pathway and thereby promote proliferation and activation of CD4+ T-cells and exacerbate age-related autoimmunity [151, 153, 154] (Fig. 4).

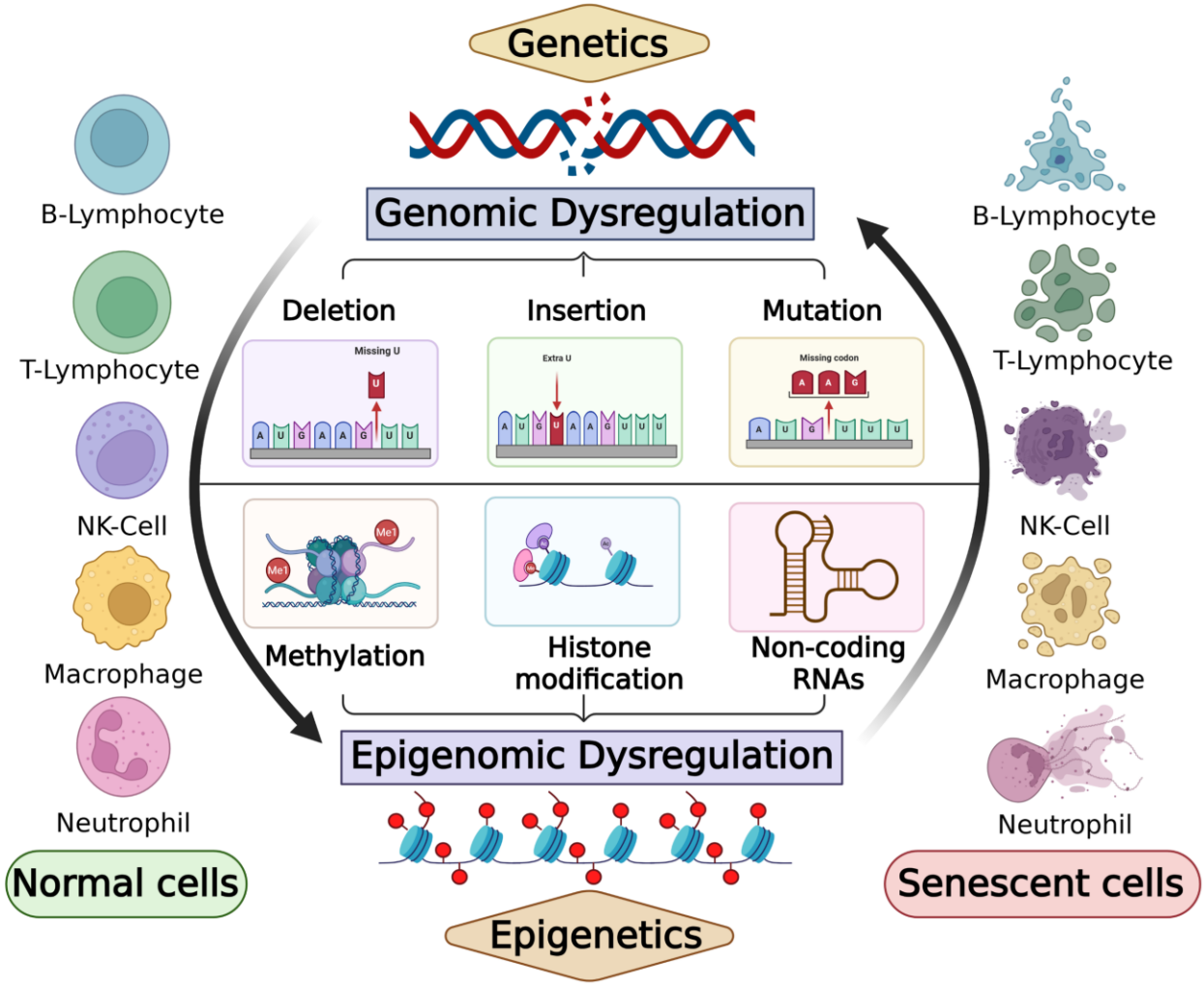

Figure 4. The role of genetic and epigenetic events in cellular senescence. A schematic model illustrates alterations of immune cells during genetic and epigenetic dysregulation. *Left* and *right* panels depict normal and affected immune B-, T-, NK-cells, macrophages, and neutrophils under nornal and senescent states, respectively. Circular arrows denote the interaction between impaired genetic and epigenetic functions in promoting cellular senescence. The *central* panel shows genetic instability that includes deletions, insertions, and mutations, all of which can alter the DNA sequence and impair cellular function. Epigenetic dysregulation is portrayed through DNA methylation, histone modifications, and non-coding RNAs, which collectively influence gene expression without altering the DNA sequence. These processes, driven by both genetic and epigenetic factors, lead to the functional decline of immune cells. Arrows indicate the interplay between genetic and epigenetic dysregulation in driving immune senescence.

Epigenetic dysregulation has been recognized as a central mechanism linking to EIS [83, 155, 156]. The epigenetic clock evolved to estimate biological age based on methylation signatures at selected CpG islands. Its utility now extends to numerous immune cell populations, including neutrophils, monocytes, and $CD4^+$ T- and B-cells. Deviations from methylation patterns indicate that epigenetic alterations not only supplement aging but also accelerate immune dysregulation [157]. During aging, global hypomethylation promotes aberrant expression of pro-inflammatory genes, while site-specific hypermethylation compromises the transcription required for lymphocyte development and activation. Critical immune regulators such as FOXN1, which guides thymic epithelial cell function and is essential for optimal T-cell signaling, are silenced with inflammaging [52, 83, 155].

Histone modifications further shape the epigenetic landscape by altering chromatin accessibility and transcriptional dynamics [83]. Age-dependent shifts in histone acetylation, methylation, and phosphorylation support activation of nuclear factor-kB (NF-κB)-driven inflammatory signaling and contribute to impaired differentiation and response of immune cells [156, 158]. These modifications underscore that epigenetic drift is a functional component of immune aging [52, 83, 156].

Non-coding RNAs add yet another dimension to epigenetic dysregulation impacting EIS. Concomitantly, microRNAs are essential for maintaining immune cell homeostasis, and their aberrant regulation disrupts T-cell activation, proliferation, and memory formation [83, 158]. Age-related decline in miR-181a modulates Sirtuin1 (SIRT1) and results in heightened replication stress and excessive inflammatory cytokine production in naïve T-cells [157]. Long ncRNAs also influence chromatin organization and contribute to chronic inflammation [83, 158]. Further support for epigenetic impact on immune aging comes from DNA methylation in individuals with autoimmune or chronic inflammatory disorders. These suggest that sustained immune activation can imprint aging-like epigenetic signatures on hematopoietic progenitors and mature immune subsets. Notably, the loci most affected often involve genes responsible for cytokine signaling, antigen processing, and lymphocyte differentiation, underscoring their potential as biomarkers and mechanistic drivers of inflammaging [159]. Key epigenetic regulators, such as DNA-methyltransferase 3A, SIRT1 and SIRT3, and the transcription factor forkhead box O3, play integral roles in maintaining genomic and mitochondrial stability and safeguarding immune cell longevity. Dysregulation of these factors enhances the accumulation of senescent pro-inflammatory cells, while persistent low-grade inflammation can further destabilize epigenetic networks, linking to EIS and age-related diseases [160].

Genomic and epigenomic instabilities, involving EIS, contribute to age-associated pathologies by impairing immune surveillance, fueling chronic inflammation, and promoting cellular transformation. In cancers, immune deficiency, characterized by DNA damage and chromatin remodeling, fosters a tumor-microenvironment and weakens immune responses to neoplastic cells [157, 161, 162]. Besides, age-driven epigenetic drift accelerates atherogenesis, fibrosis, and CVDs [163, 164]. Neurodegenerative disorders are also influenced by altered DNA methylation and histone modifications, in which inflammation driven by senescent immune cells exacerbates neurotoxicity and disease progression [165, 166]. The decline in immune competence due to genomic instability and epigenetic disarray compromises both innate and adaptive responses, leading to higher disease susceptibility, impaired pathogen clearance, and reduced vaccine efficacy in older individuals [167]. Needless to say, both genetic and epigenetic dysregulation are active drivers of many age-associated diseases, including diabetes, CVDs, and cancers, by undermining immune homeostasis.

8. Immunosenescence and Inflammaging and Their Correlation with Age-Linked Pathologies

A hallmark of immunosenescence is thymic involution**,** which reduces the production of new T- and B-cells, particularly within the naïve population [168, 169]. Concurrently, aging is associated with a low-grade inflammatory state that further disrupts the immune system [169, 170]. Dysregulation of a number of signaling pathways, including NF-κB, mTOR, JAK-STAT, AMPK, and SIRTs, plays central roles in modulating immunodeficiency. For instance, NF-κB activity increases with age due to oxidative stress and DNA damage, reducing T-cell diversity, immune surveillance, and contributing to tissue degeneration. Likewise, alterations in the JAK-STAT pathway, particularly the activation of STAT3, promote the production of pro-inflammatory cytokines, which support the development of SASP and chronic inflammation [108].

The immune system during aging is thought to represent a form of adaptation, and this remodeling process involves genetic alteration, physical activity, microbial diversity, and comorbidities that impact chronic, metabolic, and neurodegenerative diseases [170, 171], in which post-translational modifications (PTMs) of several factors are recognized. Specifically, PTMs such as methylation, acetylation, ubiquitination, and O-GlcNAcylation play essential roles in regulating proteostasis. EIS has been regarded as a detrimental event because it contributes to chronic inflammation and reduces the aging immune system's ability to mount effective antibody and cellular responses to infections [170]. Accordingly, the communication between the innate and adaptive immune systems becomes dysregulated, ultimately weakening the overall response to antigens and further accelerating the inflammatory process [169]. Macrophages express numerous receptors for danger-associated molecular patterns, which play an important role in driving localized inflammation. Older adults exhibit increased production of inflammatory cytokines, such as IL-1β, IL-6, IL-8, and tumor necrosis factor α (TNF-α), along with C-reactive protein (CRP), which are biomarkers of inflammaging. With age, the increase in free radicals amplifies chronic inflammation in a feedback loop described by the oxi-inflamm-aging theory, in which elevated ROS levels cause both DNA and mitochondrial damage, triggering cellular senescence and

SASP [169]. Impaired signaling and defective autophagy in T-cells exacerbate mitochondrial dysfunction, ROS accumulation, and expansion of myeloid-derived suppressor cells. This self-reinforcing cycle of SASP and inflammation accelerates immune aging [70] (Fig. 5).

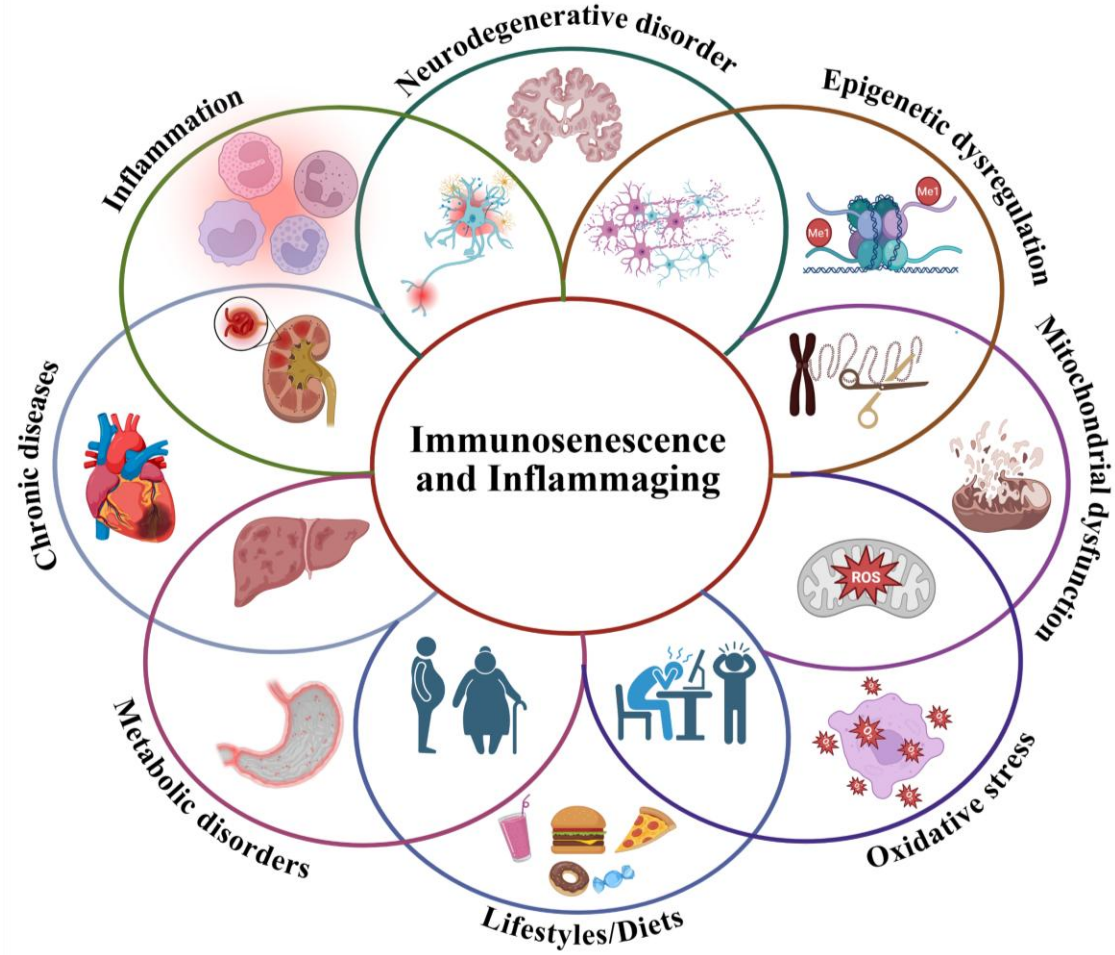

Figure 5. Influence of diverse factors and processes on immunosenescence and inflammaging. A schematic representation illustrates overlapping circles that indicate the bidirectional and interacting mechanisms. The convergence of various factors accelerates age-related disorders. The persistent inflammation and chronic diseases can sustain immune activation. Metabolic disorders, adverse dietary patterns, and unhealthy lifestyle factors further disrupt immune competence and amplify inflammatory signaling. Additionally, mitochondrial dysfunction and oxidative stress promote cellular damage and impaired immune function. Epigenetic alterations modify gene expression required for immune homeostasis, while neurodegenerative disorders are influenced by prolonged inflammatory conditions. All of these events are associated with immunosenescence and inflammaging (*center*), representing a shared outcome arising from multiple interacting signaling.

Age-linked EIS impacts diverse neurodegenerative diseases by modulating chronic inflammation that amplifies glial activation, impairs clearance of toxic proteins, and promotes neuronal injury. Elevated cytokines alter T-cell subsets and increased microglial and astrocytic reactivity create a pro-inflammatory environment, which accelerates amyloid-β (Aβ) aggregation, inflammation, and immune cell infiltration into the brain. These age-related changes, involving EIS, form a feed-forward loop that exacerbates neurodegeneration and contributes to the progression of Alzheimer's and Parkinson's diseases [56, 108, 172, 173].

Beyond neurodegenerative processes, immune dysfunction is further shaped by several interconnected mechanisms that intensify inflammation [158], in which impairment of genetic and epigenetic machineries plays an important role. Mitochondrial dysfunction adds another layer of complication, as diminished respiratory capacity, excessive ROS production, and impaired mitophagy based T-cell activation stimulate inflammasome pathways [83]. Aging induces immune changes in the cardiovascular system that promote chronic inflammation, endothelial dysfunction, oxidative stress, and vascular remodeling, leading to arterial stiffness and

plaque formation [55]. Similar immune-driven vulnerabilities appear in the skin, where aging weakens barrier integrity, enhances exposure to microbes and environmental irritants, and reduces the ability to recover injuries. These changes trigger delicate cytokine activity in the epidermis, while diminishing repair capacity and reducing adaptive responses in older individuals [174]. The decline in immune regulation, combined with inflammatory signaling and impaired tissue repair, forms a loop that deteriorates diverse physiological processes [175]. Recognizing how these interconnected mechanisms contribute to disease progression underscores the importance of targeting EIS to extend lifespan and resilience in geriatric populations (Fig. 5).

Immunosenescence also involves a gain-of-function effect, in which adaptive immune cells acquire innate-like properties that paradoxically increase autoimmune susceptibility. Senescent αβCD8+ T-cells attain innate-like activity and use acquired NK cell receptors as an alternative mechanism to mediate rapid effector functions, while losing T-cell signaling [107]. These immunosenescent T-cells upregulate receptors in NK cells, including immunoglobulin- and killer-cell lectin-like G1 activities, allowing them to exert antigen-independent effector functions and distinct secretory phenotypes [176]. Age-associated B-cells represent another critical gain-of-function event, responding to TLR7 and TLR9 stimuli and efficient autoantibody production through T-bet gene expression and the extrafollicular differentiation process [177]. Furthermore, age-associated T helper cells, a distinct CXCR3midCD4+ effector memory subset, exhibit both cytotoxic phenotype and B helper cell functions regulated by transcription factor ZEB2 [178]. These changes represent a T-cell aging-associated phenotype that exhibits both loss-of-function and gain-of-function features, transforming highly specific, clonally distributed into innate, end-differentiation, tissue invasive effector cells that promote chronic inflammation and autoimmune pathology [179]. The metabolic reprogramming involves immune dysregulation, SASP accumulation, and epigenetic changes, which foster a microenvironment, representing EIS as a catalyst for the development of autoimmune diseases [180].

9. Immunomodulatory Strategies for Combating Age-Related Diseases

Immunomodulation, amending the function of the immune system's response, is fundamental to treating a variety of health problems in aging. Recent advances in biotechnological, pharmacological, and regenerative medicine indicate that immunomodulation can be considered a novel therapeutic strategy for combating diverse age-related diseases impacted by inflammatory and autoimmune conditions. A number of key approaches that are known to restore EIS for healthy aging are briefly discussed below.

9.1. Nutrition, and macro- and micro-elements

The immune system vulnerabilities associated with aging intersect with multiple challenges, when both nutrient intake and the body's capacity to process key elements are deteriorated [181, 182]. Specifically, deficiencies in macro- and micro-elements are common in older adults and contribute to a decline in physiological activities, raising the risk of age-related diseases and mortality [182]. Since immune competence depends on healthy diets, undernutrition weakens the fundamental protective mechanisms [183]. Balanced nutrition and supplementation have become central strategies to immunomodulation. There is a growing interest in dietary approaches to support immunity in aged individuals, as nutritional interventions are often more practical and sustainable than medical therapies [184]. Nutrients that supply energy include proteins, fats, carbohydrates, essential minerals, and vitamins, all of which are increasingly recognized for their influence on immune health. Minerals such as magnesium, calcium, potassium, sodium, and phosphorus are abundant in tissues and essential for numerous biological processes; however, their deficiencies increase oxidative stress, inflammation, CVDs, and Alzheimer's Disease (AD) and AD-related dementias (ADRD) [185-187]. Potassium regulates osmotic balance, muscle and neuronal function, and immunity; while its low levels activate the NLRP3 inflammasome and raise cytokines, high levels impair T-cell activity and trigger autophagy [187, 188]. Concurrently, tryptophan, an amino acid found in protein-rich foods like eggs, fish, and meats, is essential for immune and neurological health [184, 189]. Moreover, trace elements such as zinc, selenium, iron, iodine, copper, cobalt, chromium, and manganese play equally critical roles in regulating immune response, inflammation, and autoimmunity [187].

Vitamins are essential for both cellular and immune functions, with many revealing antioxidant and anti-inflammatory properties. While humans can synthesize vitamins D, K, B3, and biotin, most vitamins are obtained through various diets. Several vitamins play important roles in epigenetic regulation; for example, folate provides methyl groups for DNA methylation, influencing inflammatory gene expression, in which vitamin B12 supports genomic stability [182, 190]. Vitamin A and its derivatives (retinoids) are central to maintaining both innate and adaptive immunity, and contribute to numerous physiological functions, including

vision, reproduction, and homeostasis. Notably, retinoids have been shown to restore disrupted neurosteroidogenesis in AD-mimetic hippocampal neuronal cells, highlighting their importance in neuronal stability during aging [191-193]. Additionally, both vitamin C and D enhance immune defense, exhibit neuroprotective effects, and maintain bone health, while also modulating genetic pathways that influence susceptibility to cancers, diabetes, and autoimmune disorders [190]. Therefore, adequate intake of macro- and micro-nutrients and amino acids helps oppose immune decline, reduce susceptibility to infections and metabolic and/or neurodegenerative disorders, and reinforce overall resilience for countering age-associated diseases (Fig. 6).

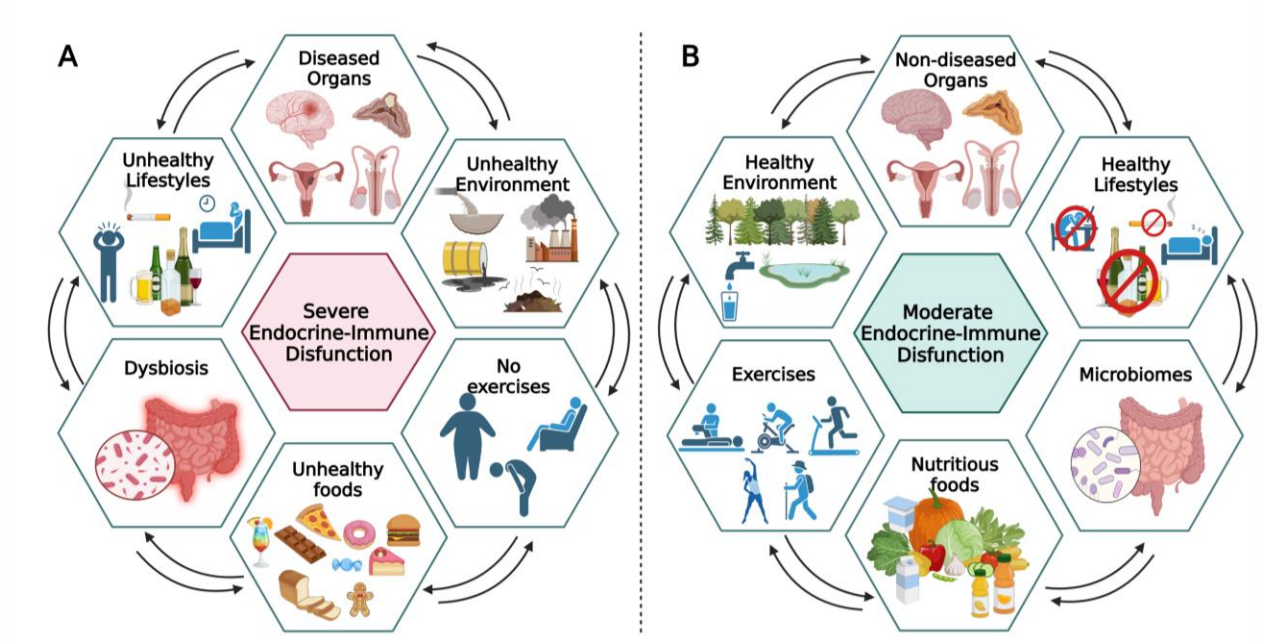

Figure 6. Alterations of a variety of factors and processes inin either severe or moderate endocrine-immune dysfunction. Hypothetical models depict the roles of multiple events and signaling in endocrine-immune dysfunction. Specifically, unhealthy lifestyles, diseased organs, poor diets, physical inactivity, dysbiosis, and unhealthy environmental factors, all of which coordinately promote immune dysfunction, chronic inflammation, and increased susceptibility to age-related diseases (*panel A*). On the other hand, *Panel B* illustratesdiverse senarios for moderate endocrine-immune dysfunction. These strategies include hormone regulation, regular physical activity, nutritious diets, healthy gut-microbiota, and favourable environmental and lifestyle conditions for maintaining immune responses of the older population.

9.2. Lifestyles

A healthy lifestyle influences immunomodulation in aged individuals. Nutritional deficits, psychological stress, sleep disturbance, and physical inactivity amplify inflammatory signaling and modulate EIS, while regular exercise and balanced diets can mitigate cytokine overproduction and enhance immune cell function [83, 158]. While people are currently living longer, many spend their later years coping with chronic illnesses and diseases [189, 194]. That reality has sharpened attention on lifestyle-based measures, sleep, stress management, smoking, alcohol, and social engagement, interventions that are powerful tools to strengthen immune suppleness [156, 189, 194]. Stress modulates EIS and is accompanied by elevated pro-inflammatory cytokines and cortisol, and decreased dehydroepiandrosterone (DHEA), levels [195, 196]. Stress management practices can counter these effects by reducing NF-κB and CRP levels and enhancing $CD4^+$ T-cells and telomerase activity [156, 197]. Alternatively, sleep deprivation elevates inflammatory markers, i.e., IL-6, IL-1β, and TNF-α, reduces vaccine responses, and increases susceptibility to infections. Besides, body weight control and caloric restriction are known to slow immune aging and reduce inflammation in the elderly [156, 198, 199]. Mechanistically, reduced calorie intake activates AMPK, suppresses mTOR, and influences AKT/PI3K, and SIRT1, all of which maintain metabolic balance [199]. It has been demonstrated that moderate caloric reduction alleviates immune responses by slowing cellular senescence, increasing thymic T-cell output, and identifying PLA2G7-mediated anti-aging effects [198]. Smoking and excessive alcohol consumption negatively influence immune function and disrupt gut microbial activity [156, 196]. By managing stress, sleep, caloric intake, and reducing smoking and alcohol use, older adults can strengthen their immune resilience. These interventions support multiple

physiological systems, lower inflammatory burden, improve metabolic and hormonal balance, and stabilize gut-immune communication (Fig. 6).

9.3. Gut-microbiota

Microbiota supports digestion, metabolic balance, and immune regulation. With aging and EIS, the gut microbial system becomes less stable, making it more vulnerable. A wide range of influences, including environmental exposures, dietary habits, and medication can alter microbial environment and function. The microbiota–gut–brain axis has gained strong attention, as it impacts immune signaling and enteroendocrine communication [196, 200]. Dysbiosis aligns with elevated circulating inflammatory markers, including NLRP3, IL-6, and IL-1β, reflecting a heightened inflammatory state [200, 201]. Besides, nutrient-sensing networks that include the hypothalamus, pituitary gland, and peripheral tissues play major roles in shaping endocrine-immune aging. This somatotropic axis relies on pathways governed by various signaling, including mTOR and AMPK, which sustain energy balance. When these signaling cascades become dysregulated, increased metabolic stress and vulnerability to chronic diseases evolve [183, 202]. Disturbances along the gut-microbiota-brain communication can promote cognitive decline and dementia by elevating inflammation [183, 203-205]. Hormones released during chronic stress can reshape the gut-microbial landscape and amplify neuronal inflammatory signaling. Overall, disturbances in gut-microbiota composition, immune activation, and endocrine regulation converge to influence neuroinflammation and accelerate cognitive decline [206].

9.4. Physical activity

Physical activity has emerged as one of the most influential lifestyle factors capable of restoring EIS [184, 199, 207]. The accumulation of late-stage effector memory cells, poor proliferative responses to mitogens, and a CD4:CD8 ratio below 1.0 are largely driven by CMV, in which exercise has been proposed to exert an anti-immunosenescence effect [208]. Routine exercise strengthens muscle quality, helps preserve bone mineral density, reduces metabolic dysfunction, and supports cognitive stability [199, 207]. Intervention studies further show that a 12-week program combining moderate aerobic and strength training can lower the proportion of non-classical $CD14^{+}/CD16^{+}$ monocyte cells often associated with heightened inflammatory and senescent profiles [184, 209, 210]. Further, older adults have reported that highly trained women demonstrate stronger mitogen-induced T-cell proliferation than their sedentary counterparts [184, 211].Immune benefits from exercise result in increases in circulating leukocytes and cytokines, which enhance cell trafficking between blood and tissues, and strengthen EIS [212]. Exercise mobilizes senescent T-cells from peripheral tissues into circulation, facilitating their apoptosis and creating a 'vacant space' for expansion of newly generated naïve T-cells, an event that helps restore the functional T-cell repertoire [213]. It also dampens chronic inflammation markers, including CRP, TNFα, IL-1β, and IL-10, and supports thymic function via effects on ILs [184, 214, 215]. Exercise engages core energy-sensing signaling such as AMPK, mTOR, and SIRT, promotes autophagy, and counteracts oxidative stress and inflammatory signaling [199]. These systemic actions not only preserve immune capability but also protect cardiovascular function by increasing blood flow, lower inflammation, and reduced oxidative stress [207]. It is worth noting that the J-shaped curve model, proposed by Nieman and Colleagues, describes how moderate-intensity exercise lowers the risk of upper respiratory tract infections below that of sedentary individuals, while prolonged or high-intensity exercise raises infection susceptibility [209, 216, 217]. Epidemiological evidence suggests that regular physical activity reduces the incidence of communicable diseases that are impacted by viral and bacterial infections [218]. Therefore, adopting a sustainable routine of physical activity, rather than sporadic intense sessions, offers the balance for preserving endocrine-immune stability during aging (Fig. 6).

9.5. Hormone profiles

Aging is associated with a gradual decline in diverse hormonal profiles, resulting in immunosenescence, and has been implicated in the progression of diverse pathologies. Specifically, hormonal shifts have profound effects on the brain, especially neuronal function, not only as systemic and metabolic regulators but also as neuromodulators that support synaptic plasticity and neuroimmune balance [219, 220]. Disruption of the endocrine milieu exacerbates neuroinflammation, weakens neuroprotective mechanisms, and destabilizes interactions between glial cells and peripheral immune signaling [221, 222]. Of note, the hormonal declines that occur during menopause and andropause reshape immune signaling and increase susceptibility to chronic diseases. Attempts have been made to reverse serum hormone levels of elderly individuals to younger levels employing hormone replacement therapies (HRTs); however, the benefit of HRTs has limited success owing to the risk of incurring long-term side effects [223, 224]. Estrogens, especially E2, exert neuroprotective effects, enhancing synaptic transmission, supporting neuronal stability, and

promoting neural stem cell proliferation [225]. They also regulate astrocyte activity, suppressing NF-κB signaling and facilitating glutamate uptake, thereby reducing excitotoxicity and free radical accumulation [226]. Similarly, androgens influence many neuronal functions via androgen receptors and indirectly through aromatization to estrogens, exerting immunosuppressive and neuroprotective effects [226]. It is noteworthy that age-related deterioration of the StAR protein, thus, sex neurosteroids, promotes AD/ADRD in women and men differently [3, 50, 51], suggesting the importance of neuroendocrine-immune deficiency in the disease pathogenesis. Interestingly, an increase in StAR levels has been reported to restore neurosteroid biosynthesis that may be beneficial for age-related cognitive impairments and dementia in aged populations. Studies have shown that excess cortisol and altered cortisol to DHEA ratios are linked to cognitive deficits, hippocampal vulnerability, and elevated risk of dementia [227, 228]. Observational and experimental data reported that loss of neurosteroids is a risk factor for cognitive decline and AD-related dementia [222, 229]. Hence, age-related deterioration in StAR-governed sex neurosteroids represents a key mechanism underlying gender-specific differences in AD/ADRD.

Based on the above considerations, it is clear that EIS functions as a framework that is coordinately linked with endocrine dysregulation, immunosenescence, inflammaging, and cellular senescence, and these events influence the development of age-related diseases. Table 1 assembles a variety of target-specific EIS biomarkers, including hormone profiles, inflammatory markers, innate immune markers, adaptive immune-cell subsets, cellular senescence, thymic-output markers, epigenetic clocks, clonal hematopoiesis markers, and frailty and functional indices, which have been discussed in respective sections with citations. While the majority of these biomarkers and their relevance to EIS have been reported to be validated, a number of them are either extrapolatory or nonspecific, in various categories (Table 1).

Table 1. A list of target-specific EIS biomarkers, ranging from hormones to frailty indices, and their correlation with the identification of diverse consequences.

Types	Biomarkers	Relevance to EIS	Status
Hormone profiles	Cortisol (diurnal rhythm, cortisol awakening response)	HPA-axis activity, stress response, immune regulation	Validated
	DHEA/DHEA-S	Counter-regulatory hormone to cortisol; age-related decline	Validated
	Testosterone and estrogens	Sex-specific reproductive aging and immune modulation	Validated
	LH, FSH, and GnRH	HPG-axis function and reproductive senescence	Validated
	TSH, T4, and T3	Thyroid function and metabolic regulation	Validated
	GH and IGF-1	Anabolic signaling and tissue maintenance	Validated
Inflammatory markers	IL-6	Chronic low-grade inflammation	Validated
	TNF-α	Pro-inflammatory cytokine associated with multimorbidity	Validated
	IL-1β	Innate inflammatory activation	Validated
	CRP	Systemic inflammation	Validated
	SASP cytokines and chemokines	Cellular senescence	Exploratory
Innate immune markers	NK-cells and cytotoxicity	Immune surveillance, aging, and immunosenescence	Validated
	Monocyte subsets (classical/intermediate/non-classical)	Inflammatory activation and immunosenescence	Exploratory
	Neutrophil-to-lymphocyte ratio (NLR)	Systemic inflammatory state	Nonspecific
Adaptive immune-cell subsets	CD4+/CD8+ ratio	Hallmark of immune aging	Validated
	Naïve T-cells (CD4+ and CD8+)	Thymic function and immune competence	Validated
	Memory/effector T-cells	Antigen exposure and immune remodeling	Validated
	Senescent T-cells (CD28−, CD57+, and KLRG1+)	Immunosenescence	Validated
	Tregs	Immune tolerance and age-related dysregulation	Validated
	B-cell subsets	Humoral immune aging	Exploratory
Cellular senescence	p16INK4a expression	Canonical marker of cellular senescence	Validated
	p21CIP1 expression	Cell-cycle arrest and senescence	Validated

	Senescence-associated β-galactosidase (SA-β-gal)	Cellular senescence detection	Validated
	Telomere length	Replicative aging	Validated
Thymic-output markers	T-cell receptor excision circles (TRECs)	Thymic output and immune renewal	Validated
	Recent thymic emigrants (RTEs)	Newly generated T-cell populations	Validated
Epigenetic clocks	Horvath DNAmAge	Biological aging	Validated
	Hannum clock	Epigenetic age estimation	Validated
	PhenoAge	Aging and disease-risk prediction	Validated
	GrimAge	Mortality and health span prediction	Validated
Clonal hematopoiesis markers	CHIP-associated mutations (DNMT3A, TET2, ASXL1, and JAK2)	Age-related hematopoietic clonal expansion and inflammation	Validated
	Variant allele frequency	Magnitude of clonal hematopoiesis	Validated
Frailty and functional indices	Frailty Phenotype (Fried criteria)	Clinical manifestation of biological aging	Validated
	Frailty Index	Deficit accumulation and biological aging	Validated
	Gait speed	Functional decline and aging	Validated
	Grip strength	Physical resilience and sarcopenia	Validated
	Short Physical Performance Battery (SPPB)	Functional capacity	Validated
	Activities of Daily Living (ADL/IADL)	Functional independence	Validated

10. Immunomodulation: A Key Therapeutic Strategy to Healthy Aging

The aging endocrine-immune system experiences progressive remodeling, which weakens the body's capacity to mount effective responses, resulting in diminished vaccine efficacy and tissue repair, and a higher propensity for chronic diseases, including CVDs, neurodegeneration, metabolic dysfunction, and malignancies. As global life expectancy continues to rise, the burden of age-associated disorders has expanded in parallel, leading to greater functional decline, reduced independence, and higher reliance on healthcare resources. The cumulative impact of EIS and physiological challenges underscores the critical need for immunomodulation for the quality living of geriatric populations [230, 231]. Although aging inevitably dampens endocrine-immune function, targeted strategies can restore the body's defense mechanisms. A strong immune system serves as preventive medicine against diverse age-related diseases. Studies have shown that dietary modifications should begin well before the visible onset of aging, as physiological decline in various systems can emerge as early as the fourth decade of life [182, 207]. Micronutrients such as vitamins A, C, D, and E, along with copper, iron, selenium, and zinc, are critical for sustaining immune cell function, reducing infection risk, and enhancing vaccine responsiveness. Probiotics also contribute to immune resilience by modulating gut-microbiota and short-chain fatty acids, yielding cardiometabolic benefits, reducing oxidative stress and inflammation [182, 207]. Older adults who maintain social networks demonstrate lower levels of systemic inflammation, reduced incidence of depression, and improved resilience to infections, highlighting the interplay between psychosocial well-being and immune function [156, 232]. In contrast, social isolation and limited mobility exacerbate chronic inflammatory states and accelerate EIS, resulting in the development of age-related diseases (Fig. 7).

Other lifestyle components, such as adequate sleep, support cytokine production, memory T-cell formation, and metabolic recovery. Effective stress management, through meditation, yoga, and exercise, reduces cortisol and helps maintain immune function. Pharmacological and therapeutic strategies provide a variety of targeted approaches to counter EIS, particularly through anti-inflammatory interventions. Emerging advances, including immunomodulatory therapies, age-specific vaccines, and gut-microbiota maintenance, enhance immune responsiveness and protection against infections. Current understanding of EIS and its impact on age-associated pathologies indicates that immunomodulatory strategies, involving nutritional, immunotherapeutic, and pharmacological, substances can restore a variety of those diseases for healthy aging (Table 2). Importantly, age-related intervention approaches in mitigating EIS often require a combinatorial action for substantial clinical outcomes.

11. Conclusions and Future Directions

EIS, modulating genomic, epigenomic, mitochondrial, and metabolic functions, has been linked with a variety of age-associated diseases. Consequently, immuno-modulatory strategies are the key to quality living of the

geriatric population. Since the decline of endocrine and immune signaling disrupts bodily homeostasis, EIS represents an important therapeutic approach for countering many hallmarks of aging, targeting hormonal imbalance, mitochondrial dysfunction, and genetic and epigenetic dysregulation [155, 233].

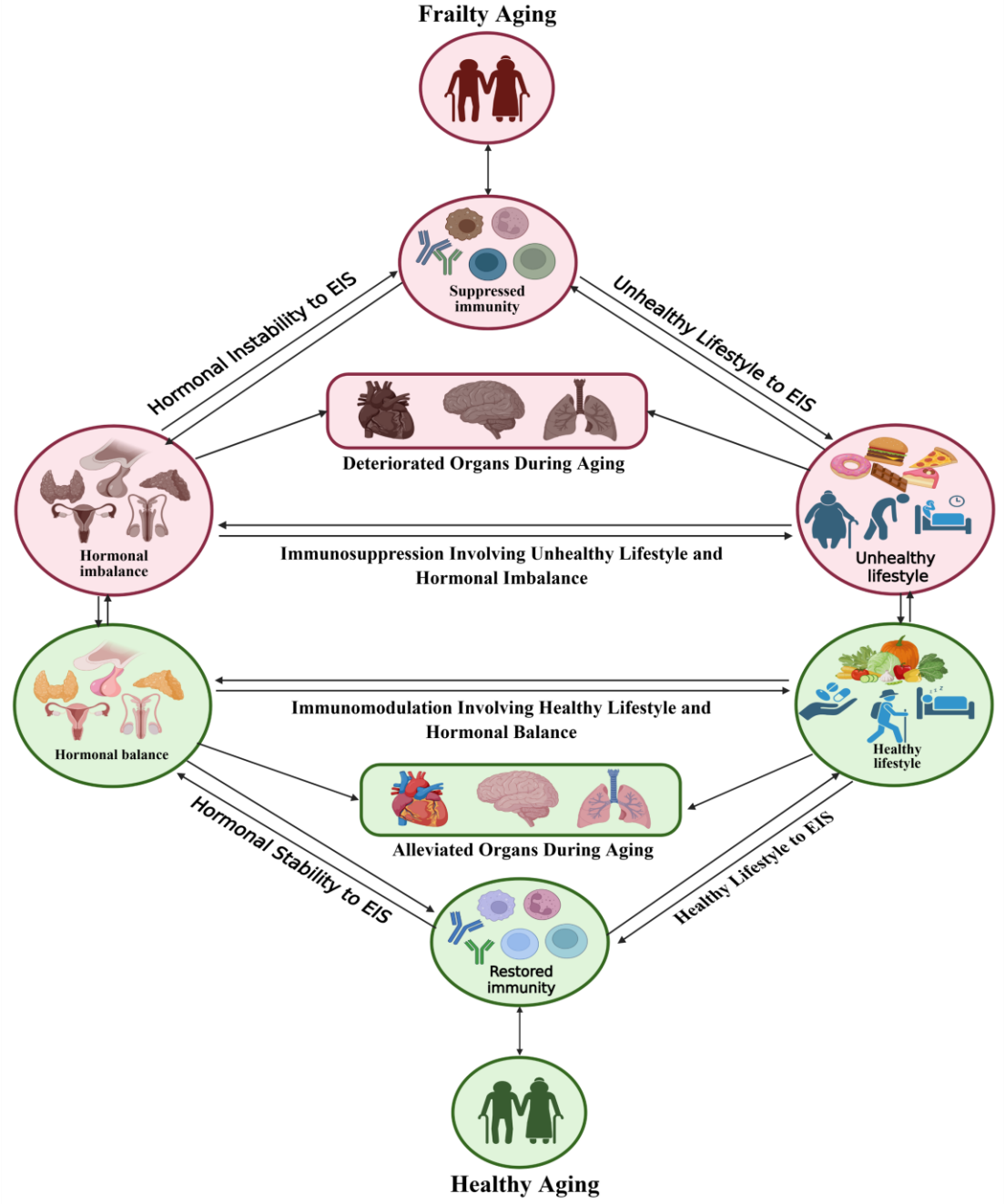

Figure 7. Involvement of EIS in frailty aging and role of immunomodulation in healthy aging. A schematic representation illustrates the relationship between two trajectories of aging, involving immunosuppression and immunomodulation. Frailty aging is largely associated with unhealthy lifestyle factors and endocrine imbalance, which converge to induce immune suppression, leading to progressive and functional deterioration of vital organs like heart, brain, and gonads (*upper panel*). In contrast, immunomodulatory strategies, involving hormonal stability, regular physical activity, healthy diets, gut-microbiome, and favourable environmental and lifestyle conditions, contribute to healthy aging (*lower panel*). Both endocrine and immune-based diverse events play important roles in frailty and healthy aging.

Clinical consequences are often more inflammatory yet less reliably protective, increasing vulnerability to infection and limiting vaccine performance, while contributing to chronic diseases. EIS weakens host defense against infections and substantially influences the development and progression of age-linked disorders, including CVDs, neurodegenerative diseases, and cancers. Immune aging is shaped by a complex interplay of genetic predisposition, epigenetic drift, metabolic status, endocrine dysfunction, and environmental exposures [49]. Of note, immunosenescence entails both compromised innate and adaptive activities, including thymic involution, diminished naïve T-cell output, and expansion of senescent phenotypes, which coincide with elevated cytokines and a low-grade inflammation. Age-related metabolic and endocrine dysregulation, mitochondrial dysfunction, and chronic activation of pro-inflammatory signaling modulate EIS, reinforce inflammaging, and weaken immune resilience [17, 108, 234].

Table 2: Influence of EIS on a variety of disorders and their restorative levels with immunomodulatory strategies for extending lifespan and healthy aging.

Pathologies	EIS	Immunomodulation	References
Aging	+++	+++	[131, 235, 238]
AD/ADRD	+ + +	++	[239-241]
Neurodegenerative Diseases	+++	++	[242, 243]
Obesity	+ + +	+ +	[116, 244, 245]
Diabetes	+ + +	++	[123, 246]
Cancers	+++	++	[247-249]
CVDs	+++	++	[198, 235]
Cushing's Disease	++	+	[250, 251]
Metabolic Disorders	+++	++	[206, 252]
Addison's Disease	++	+	[253, 254]
Lipoid CAH	++	+	[3, 255, 256]
Hypo & Hyper-Thyroidisms	+++	++	[257-259]
Endometriosis	+++	++	[260]
COVID-19	+ +	+ +	[190, 261, 262]
Osteoporosis	+ + +	++	[263, 264]
Gonadal Dysgenesis	+++	++	[235, 265, 266]

Efficiency levels: +, low; ++, medium; and +++, high to very high

The identification of the molecular and cellular mechanisms underlying endocrine-immune dysfunction helps develop therapeutic interventions for the management of age-related disorders. Given the involvement of diverse events and/or processes, an imminent challenge is to find the right combination of treatments with limited side effects, which are even more complicated with hormone-driven variations associated with menopause and andropause in women and men, respectively. Additional studies are needed to elucidate how gender-specific differences in aging contribute to pathologies in female and male mice and how those findings translate to humans. Early detection of EIS inflicted consequences, monitoring specific hormonal, senescence, inflammatory markers, and frailty indices, can mitigate many common disorders, including CVDs, AD/ADRD, and infections, for healthy aging. As such, immunomodulatory strategies are essential to restore bodily homeostasis and to reduce age-related pathologies [235]. Consequently, a hypothetical model unifying diverse scenarios, including upstream drivers, intermediate mechanisms, immunomodulatory strategies, and immune outcomes, and their relevance to clinical consequences, is proposed in Fig. 8. Precise understanding of these processes will develop tools that can detect, modulate, or eliminate senescent immune cells and may open a new avenue to extend lifespan in managing age-related diseases.

The multifactorial framework of EIS and its correlation with disease onset, incidence, and severity requires targeted therapies for healthy aging. A growing body of evidence highlights the pivotal role of modifiable factors that can alleviate both endocrine and immune trajectories. Unhealthy diets, physical inactivity, psychological stress, and poor sleep quality are associated with inflammation and accelerated immune decline. Conversely, diets rich in vitamins and antioxidants, along with adequate intake of nutrients, are linked to improved endocrine-immune competence and reduced systemic inflammation in older adults [236, 237]. Regular physical activity exerts broad protective effects by enhancing immune surveillance, attenuating chronic inflammation, and improving vaccination response [184]. In parallel, stress reduction and sleep optimization support

neuroendocrine-immune regulation and sustain healthy physiology. Targeted immunomodulatory approaches for EIS involve macro- and micro-elements and healthy lifestyles/activities, which hold promise for restoring bodily homeostasis in aging.

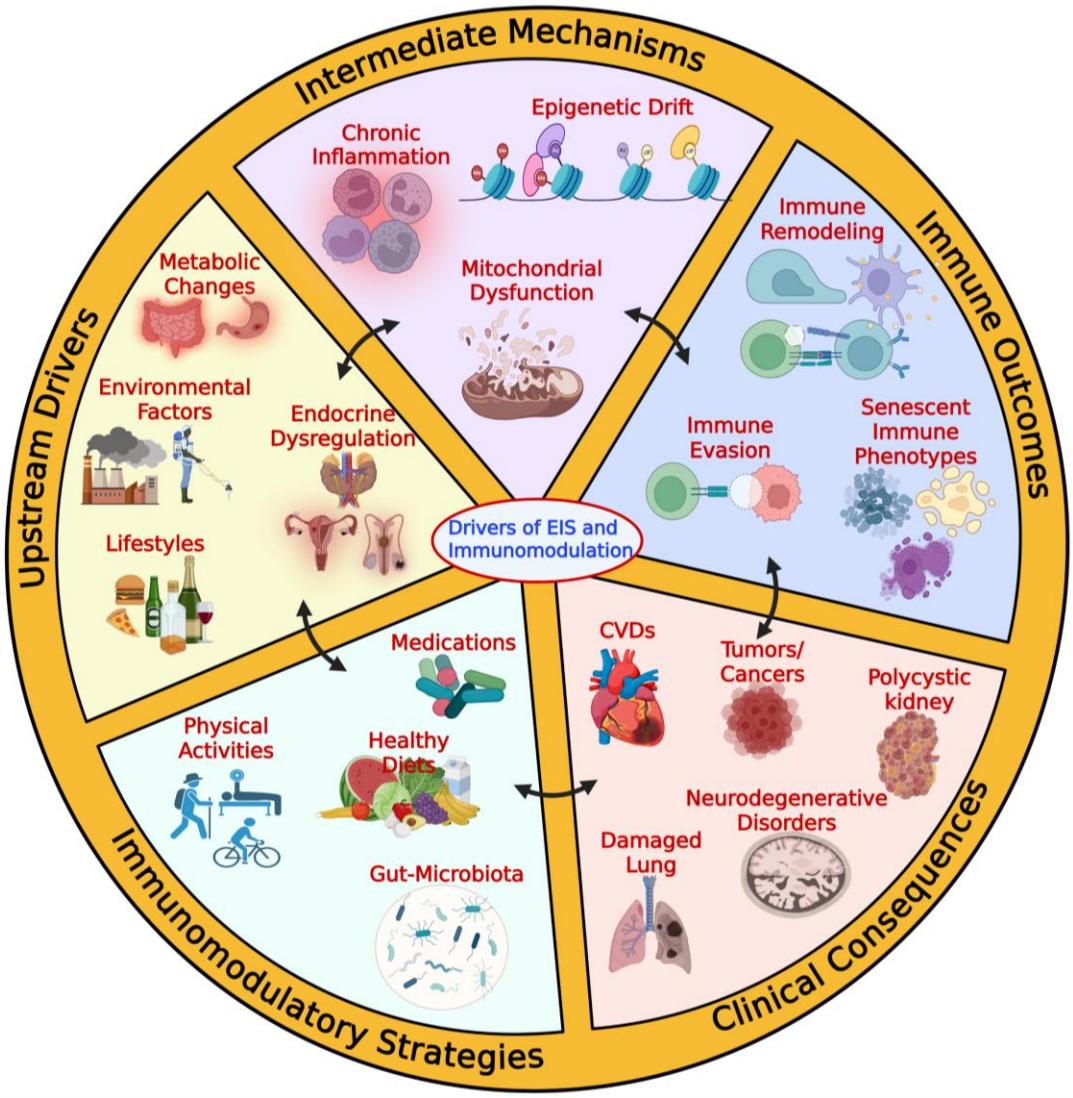

Figure 8. The unifying core drivers of EIS and the immunomodulatory landscape. A schematic model depicts five interconnected scenarios that are coordinately associated with both EIS and immunomodulation. Specifically, upstream rivers, endocrine dysregulation, metabolic shifts, environmental pollutants, and lifestyle factors converge to initiate age-associated perturbations in immune homeostasis. Intermediate mechanisms input channel through molecular and cellular axes, such as inflammaging, epigenetic drift involving aberrant DNA methylation and histone remodeling, and mitochondrial dysfunction, which together reprogram immune cell identity and longevity. Immune outcomes encompass remodeling of innate and adaptive immune compartments, accumulation of senescent phenotypes (including exhausted T-cells, dysfunctional B-cells, and pro-inflammatory macrophages), and progressive failure of immunosurveillance. With clinical consequences, these immune alterations ultimately manifest as major age-associated pathologies, including CVDs, cancers, and neurodegenerative disorders. Immunomodulation constitutes strategies that involve physical activity, healthy dietary patterns, pharmacological agents, and gut-microbiota for restoring/reversing EIS. The bidirectional arrows denote the self-amplifying feedback loops operating between inflammation, epigenetic reprogramming, and mitochondrial dysfunction, suggesting that endocrine-immune dysregulation is not linear, but rather a dynamic, reciprocally reinforced, and therapeutically modifiable process.

These strategies underscore a paradigm shift in research for managing diverse diseases by restoring EIS, which promotes the well-being of aging populations. Moreover, personalized therapies are impactful in conserving immune function, which ultimately reduces age-related diseases and supports healthy aging across the

lifespan. Despite the multifaceted advancements, there are gaps in understanding of the impact of EIS in gender-specific disease processes, in which outcomes will be instrumental for personalized treatments. Clinical and/or longitudinal studies with women and men are warranted to thoroughly evaluate a combination of EIS-targeted therapies, including nutritional (e.g., macro- and micro-elements), pharmacological (e.g., HRTs and targeted drugs), and/or immunological (e.g., lifestyles and vaccinations), which will yield effective intervention strategies for the well-being of geriatric populations.

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Declaration of Interest

The authors declare that there are no competing interests that could be perceived as prejudicing the impartiality of this work.

Author Contributions

Conceptualization, project administration, literature review, and supervision: PM. Writing, drafting, and reviewing: PRM, SY, CM, HK, and PHR. All authors have read and agreed to the final version of the manuscript for publication.

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