Aging and Disease
www.aginganddisease.org
Early access date: April 24, 2026
http://dx.doi.org/10.14336/AD.2025.1557

Review

Inflammaging: From Mechanisms to Clinical Implications and Targeted Interventions

Rola S. Zeidan[1,2], Aditya S. Shirali[3], Simon Reinhard[2], Anna Picca[4,5], Patricia Vial[6], Lisiane Pruinelli[7], Joe G.N. Garcia[8], Christian Leeuwenburgh[9], Stephen Anton[1*]

[1]Department of Physiology and Aging, College of Medicine, University of Florida, Gainesville, Florida, USA. [2]Department of Health Outcomes and Biomedical Informatics, College of Medicine, University of Florida, Gainesville, Florida, USA. [3]Division of Surgical Oncology, Department of Surgery, College of Medicine, University of Florida, Gainesville, Florida, USA. [4]Department of Medicine and Surgery, LUM University, Casamassima, Italy. [5]Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy. [6]Panamanian Association for the Prevention and Treatment of Obesity, Panama, Republic of Panama. [7]Department of Biobehavioral Nursing Science, College of Nursing, University of Florida, Gainesville, Florida, USA. [8]Center for Inflammation Science and System Medicine, UF Herbert Wertheim Scripps Research Institute, Jupiter, Florida, USA. [9]Department of Medicine, Division of Geriatric Medicine, College of Medicine, University of Florida, Gainesville, Florida, USA.

[Received December 22, 2025; Revised April 6, 2026; Accepted April 7, 2026]

ABSTRACT: Inflammaging refers to the chronic, low-grade, sterile inflammatory state that emerges as a hallmark of biological aging and is increasingly recognized as a contributor to functional decline, frailty, and the progression of multiple age-associated diseases. While acute inflammation supports host defense and tissue repair, persistent and unresolved inflammatory signaling promotes tissue damage, metabolic dysregulation, and impaired immune homeostasis. Inflammaging reflects a dysregulated physiological state associated with elevated damage-associated molecular patterns (DAMPs), pro-inflammatory cytokines, altered immune cell composition, metabolic imbalance, and the accumulation of senescent cells exhibiting a senescence-associated secretory phenotype (SASP). Together, these processes impair immune surveillance, increase oxidative stress, and tissue vulnerability, potentially accelerating functional decline and amplifying disease trajectories that may originate earlier in life. Despite ongoing challenges in precisely defining and measuring inflammaging, evidence suggests that its development is shaped not only by chronological aging but also by behavioral, environmental, psychosocial, and genetic factors, highlighting its dynamic and potentially modifiable nature. In this review, we distinguish inflammaging from general chronic inflammation, synthesize current understanding of its biological origins and mechanistic drivers, and examine its role in clinical outcomes including sarcopenia, neurodegeneration, and cardiovascular disease. We propose a conceptual translational framework linking biological mechanisms of inflammaging to multilayer biomarker signatures, AI-based risk stratification, and precision interventions. Additionally, we discuss the opportunities and limitations of these approaches for identifying individuals at risk for chronic disease and informing multi-dimensional strategies to promote resilience and extend health-span.

Keywords: Inflammation, Aging, Senescence, Age-Related Pathologies, Precision Medicine

1. Introduction

Inflammaging, the term coined by Franceschi in 2000 [1], refers to the low-grade and chronic inflammatory process that develops progressively with age in the absence of infection (i.e., sterile inflammation) [2]. This persistent inflammatory state is marked by dysregulated innate immunity that results in sustained levels of elevated

***Correspondence should be addressed to:** Dr. Stephen Anton, Department of Physiology and Aging, College of Medicine, University of Florida, Gainesville, FL, USA. Email: santon@ufl.edu

Copyright: © 2026 Zeidan RS. et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

systemic inflammatory mediators, which contribute to gradual declines in immune function and immune surveillance that ultimately compromises the body's ability to respond to internal and external threats [3, 4]. Inflammaging is increasingly recognized as a major contributor to the progression and exacerbation of several age-related diseases, including sarcopenia, neurodegenerative disorders, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, cardiovascular diseases, and diabetes, thus accelerating age-related functional decline and reducing longevity [5–8].

The trajectory and severity of inflammaging are not solely determined by chronological age but represent a complex and dynamic interplay between biological aging processes and modifiable factors across the life course. Behavioral, environmental, genetic, and psychosocial factors all converge to influence an individual's inflammatory burden, and consequently, their vulnerability to chronic disease, cognitive impairment, frailty, and premature mortality [9–11].

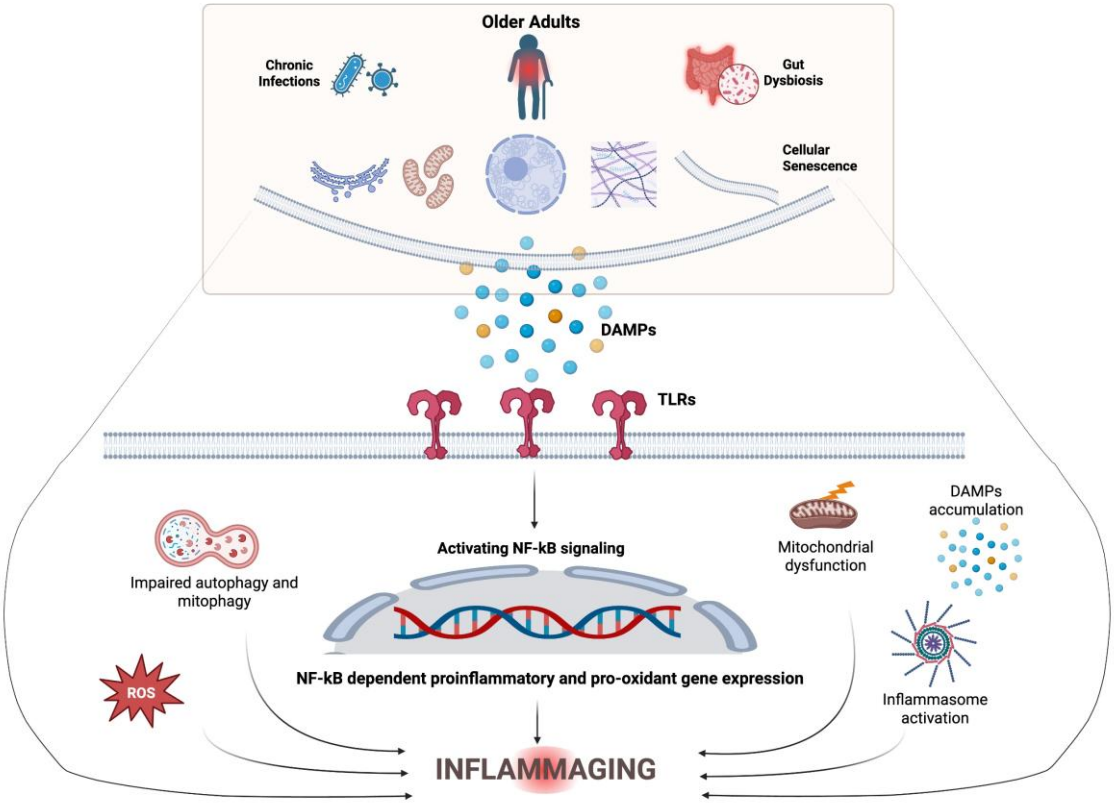


Figure 1. Cellular Drivers of Inflammaging. In older adults, chronic infections, gut dysbiosis, and the accumulation of cellular senescence act as upstream drivers of sterile and non-sterile inflammatory stress, increasing the release and accumulation of DAMPs from damaged cellular components. These circulating DAMPs engage pattern-recognition receptors, including Toll-like receptors (TLRs) at the plasma membrane to activate NF-κB, driving pro-inflammatory and pro-oxidant gene expression. Altogether, in parallel with mitochondrial dysfunction and impaired autophagy/mitophagy, elevated ROS accumulation amplifies inflammasome activation, creating a loop that feeds cellular and systemic inflammation, exacerbating inflammaging.

Recent evidence underscores the importance of chronic inflammation as a biomarker of aging with reduced levels of inflammatory markers serving as strong predictors of healthy aging in semi-supercentenarians (age ≥105 years) [12]. Additional studies have shown that inflammaging arises from a complex network of immune dysregulation, metabolic imbalance, and the accumulation of senescent cells [3, 13, 14]. Dysregulated cytokine production, both pro- and anti-inflammatory, is a hallmark of the aging immune system and contributes to a maladaptive immune profile over time [15, 16]. Additionally, senescent cells, which have permanently exited the cell cycle, accumulate with age and often acquire a pro-inflammatory phenotype known as the senescence-associated secretory phenotype (SASP), further amplifying systemic inflammation [17].

Concurrently, age-related metabolic changes, including increased adiposity and impaired glucose regulation, as well as mitochondrial dysfunction, immuno-senescence, gut dysbiosis, and chronic

infections, exacerbate this inflammatory milieu [18–20] (Fig. 1). Crucially, the clinical consequences of inflammation vary depending on the tissues affected [21]. In fact, chronic inflammation has been implicated in the etiology and progression of diverse conditions such as neurodegeneration in the central nervous system, cardiovascular disease [22, 23], cancer [24], liver disease [25], and inflammaging-related worsening of age-related lung diseases [26–29].

Previous reviews have established chronic inflammation as strongly associated with elevated disease risk and pathological aging processes [30–32]. To advance this field, the present review seeks to build upon prior work by: a) delineating the differences between general chronic inflammation and the specific biology of inflammaging; b) describing the key molecular and cellular mechanisms underpinning inflammaging; c) exploring the clinical implications of inflammaging in the context of age-related syndromes; d) discussing current therapeutic strategies to mitigate the pathobiology of inflammaging; and e) highlighting AI-informed risk prediction and proposing a conceptual translation framework that leverages AI and machine learning (ML) to integrate mechanistic pathways with biomarker signatures to identify inflammaging endotypes and guide precision interventions. This integrated framework uniquely positions our review to bridge mechanistic biology with data-driven precision medicine strategies, offering a perspective not addressed in prior literature.

2. Disentangling chronic inflammation and inflammaging

Both chronic inflammation and inflammaging involve a persistent inflammatory state. Important nuances exist, however, that are critical to understanding their respective pathobiologies. Short-lived, beneficial acute inflammation promotes wound or tissue healing. In contrast, chronic inflammation is a prolonged and maladaptive inflammatory response lasting for months or even years, leading to persistent active inflammation, hindering tissue repair and reducing host immune responsiveness and efficacy [33]. Chronic inflammation ensues as a response to unresolved infections, physical or chemical irritant exposures, and is clearly influenced by multiple factors that include genetic vulnerability, autoimmune disorders, and/or metabolic conditions (e.g., obesity, diabetes) [34–36].

Inflammaging represents a subset of chronic inflammation and is characterized by an upregulated inflammatory response within the context of biological aging [37, 38]. The severity of the chronic inflammation varies with its etiology, whereas inflammaging represents a low-grade, sterile, and persistent inflammatory state associated with aging [9, 39]. While chronic inflammation can occur at any age and can be either systemic or localized and confined, the hallmark of inflammaging is its systemic nature in older adults. This sterile inflammatory state affects multiple tissues and organs, as sterile inflammation is closely intertwined with the aging process, age-related diseases, and accelerated progression of various age-related pathologies [5, 40, 41].

Although the precise etiology of inflammaging remains poorly understood, various factors including immunosenescence, genetic predisposition, age-related tissue damage and cellular waste accumulation, and potentially chronic infections (viral, such as CMV) are linked to its development [42, 43]. Despite its association with adverse outcomes, such as frailty and increased mortality risk, inflammaging can manifest in older adults without overt clinical disease [44].

Predictably, chronic inflammation and inflammaging overlap with worsening age-related diseases, including cardiovascular diseases, cancer, chronic kidney disease, dementia, osteoporosis, sarcopenia, and frailty [5, 45]. Addressing the underlying mechanisms of inflammaging (described below), such as reducing cellular senescence and improving immune function, is a key focus in research aimed at promoting healthy aging and reducing the burden of age-related diseases [9, 32]. Understanding the unique features that distinguish chronic inflammation from inflammaging is vital for developing targeted interventions to improve health and well-being in older adults, yet these distinctions require further investigation.

3. Pathobiology of inflammaging

3.1. Overview and Biological Origins – Endogenous Signals

Among the key biological drivers of inflammaging are processes that are considered fundamental hallmarks of aging, including mitochondrial dysfunction, impaired proteostasis, cellular senescence, and metabolic dysregulation [1]. These alterations lead to the persistent release of endogenous molecules that activate innate immune pathways even in the absence of infection. Among these molecular triggers are damage-associated molecular patterns (DAMPs), such as high mobility group box 1 (HMGB1), extracellular nicotinamide phosphoribosyltransferase (NAMPT), and S100 calcium-binding proteins A8 and A9 (S100A8/9) (Fig. 1 and 2), that serve as critical endogenous molecular signals released from stressed, damaged or dying cells [46–48]. DAMPs serve as “danger” signals that alert and activate the innate immune system via engagement with pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), the cyclic guanosine monophosphate–adenosine mono-

phosphate (GMP-AMP) synthase–stimulator of interferon genes (cGAS-STING) pathway, and the nucleotide-binding leucine-rich repeat containing protein 3 (NLRP3) inflammasome, thereby initiating or amplifying a sterile inflammatory response aimed at tissue repair and homeostasis restoration [49, 50]. While this response is adaptive in the short term, sustained or unresolved DAMP signaling drives chronic, maladaptive immune activation, ultimately contributing to tissue dysfunction and age-related disease [48]. Additionally, mitochondrial dysfunction with aging further exacerbates this process by increasing reactive oxygen species (ROS), which cause oxidative damage to DNA, lipids, and proteins [50]. Impaired mitophagy, which is the selective clearance of damaged mitochondria, leads to the accumulation of dysfunctional mitochondria, amplifying oxidative stress and fueling chronic inflammation [47]. Age-related declines in autophagic clearance further contribute to the accumulation of damaged cellular components, reinforcing pro-inflammatory signaling [18–20]. Collectively, age-related metabolic changes, along with mitochondrial dysfunction, cellular senescence, immunosenescence, gut dysbiosis, and persistent low-grade infections, all contribute to inflammaging [18–20] (Fig. 1). In contrast to chronic inflammation, which is often localized and disease-specific, inflammaging is systemic, persistent, and low-grade, progressively impairing tissue resilience and repair capacity with age. Explicitly, inflammaging differs from classical chronic inflammation in that it arises in the absence of overt infection or autoimmune activation and is instead driven by cumulative, low-grade, sterile immune stimulation from endogenous sources such as DAMPs, senescent cells, and metabolic stress. Below, we will discuss some of these contributors in detail.

3.2. Role of Cellular Senescence and Senescence-Associated Secretory Phenotype (SASP)

Senescent cells are viable, non-proliferative cells resistant to apoptosis that increase with age and accumulate in various tissues [51] while adopting a proinflammatory phenotype and exhibiting increased SASP production [52, 53] (Table 1). While the SASP is thought to be tissue-specific and context-dependent, the majority of our current understanding comes from oncogene- or radiation-induced senescence models, with limited data on naturally aged human tissues [54, 55]. The mechanisms underlying age-related SASP transformation are continuing to be explored by the availability of genetically-engineered mouse models and humans studies that have examined plasma-based senescence biomarkers [56–58].

Table 1. Major Constituents of the Senescence-Associated Secretory Phenotype (SASP).

Functional Category	Representative Factors	Primary Functions / Effects
Proinflammatory cytokines	IL-1α, IL-1β, IL-6, TNF-α	Drive chronic inflammation, reinforce senescence, and recruit immune cells.
Chemokines	CCL2 (MCP-1), CCL5 (RANTES), IL-8 (CXCL8), CXCL1, CXCL10	Recruit neutrophils, monocytes/ macrophages, and T cells; shape the local immune microenvironment.
Growth factors	VEGF-A, HGF, TGF-β, IGFBP-3, IGFBP-7	Influence tissue remodeling, angiogenesis, and cell survival.
Proteases / ECM Remodeling enzymes	MMP-1, MMP-3, MMP-9, MMP-13, uPA	Degrade extracellular matrix components, alter tissue architecture, and promote invasion or fibrosis.
Other secreted factors/ regulators	HMGB1, PAI-1 (SERPINE1), GDF15	Modulate inflammation, metabolic regulation, and systemic aging phenotypes.
Non-protein mediators	ROS, prostaglandins (e.g., PGE2)	Contribute to oxidative stress and paracrine senescence signaling.

Abbreviations: Interleukin (IL)-1α, IL-1β, IL-6, and tumor necrosis factor-α (TNF-α); chemokine (C-C motif) ligand 2 (CCL2, also known as monocyte chemoattractant protein-1, MCP-1), CCL5 (regulated on activation, normal T-cell expressed and secreted, RANTES), IL-8 (C-X-C motif chemokine ligand 8, CXCL8), CXCL1, and CXCL10; vascular endothelial growth factor-A (VEGF-A), hepatocyte growth factor (HGF), transforming growth factor-β (TGF-β), insulin-like growth factor-binding protein-3 (IGFBP-3), and IGFBP-7; matrix metalloproteinases (MMP)-1, MMP-3, MMP-9, MMP-13, and urokinase-type plasminogen activator (uPA, also known as PLAU); high-mobility group box 1 (HMGB1), plasminogen activator inhibitor-1 (PAI-1, also known as serpin family E member 1 - SERPINE1), and growth differentiation factor 15 (GDF15); reactive oxygen species (ROS) and prostaglandins such as prostaglandin E2 (PGE2).

Importantly, the SASP contributes to a proinflammatory tissue environment, disrupts normal cell signaling, and impairs tissue regeneration. Senescence and the SASP, however, also play indispensable and beneficial roles in certain cases. This includes tumor suppression, wound healing, tissue remodeling, and embryonic development [59–62] where transient senescent cell accumulation and tightly regulated SASP

signaling can promote immune-mediated clearance of damaged cells and facilitate tissue repair. In this regard, indiscriminate suppression or elimination of senescent cells may disrupt physiological processes essential for tissue homeostasis and regeneration, highlighting the need to distinguish harmful chronic senescence from adaptive, transient senescence. Interestingly, circulating SASP-related proteins, such as Vascular Endothelial Growth Factor A (VEGFA), Growth Differentiation Factor 15 (GDF15), and osteopontin have been associated with physical decline in older adults, as demonstrated by our group and others [57, 58].

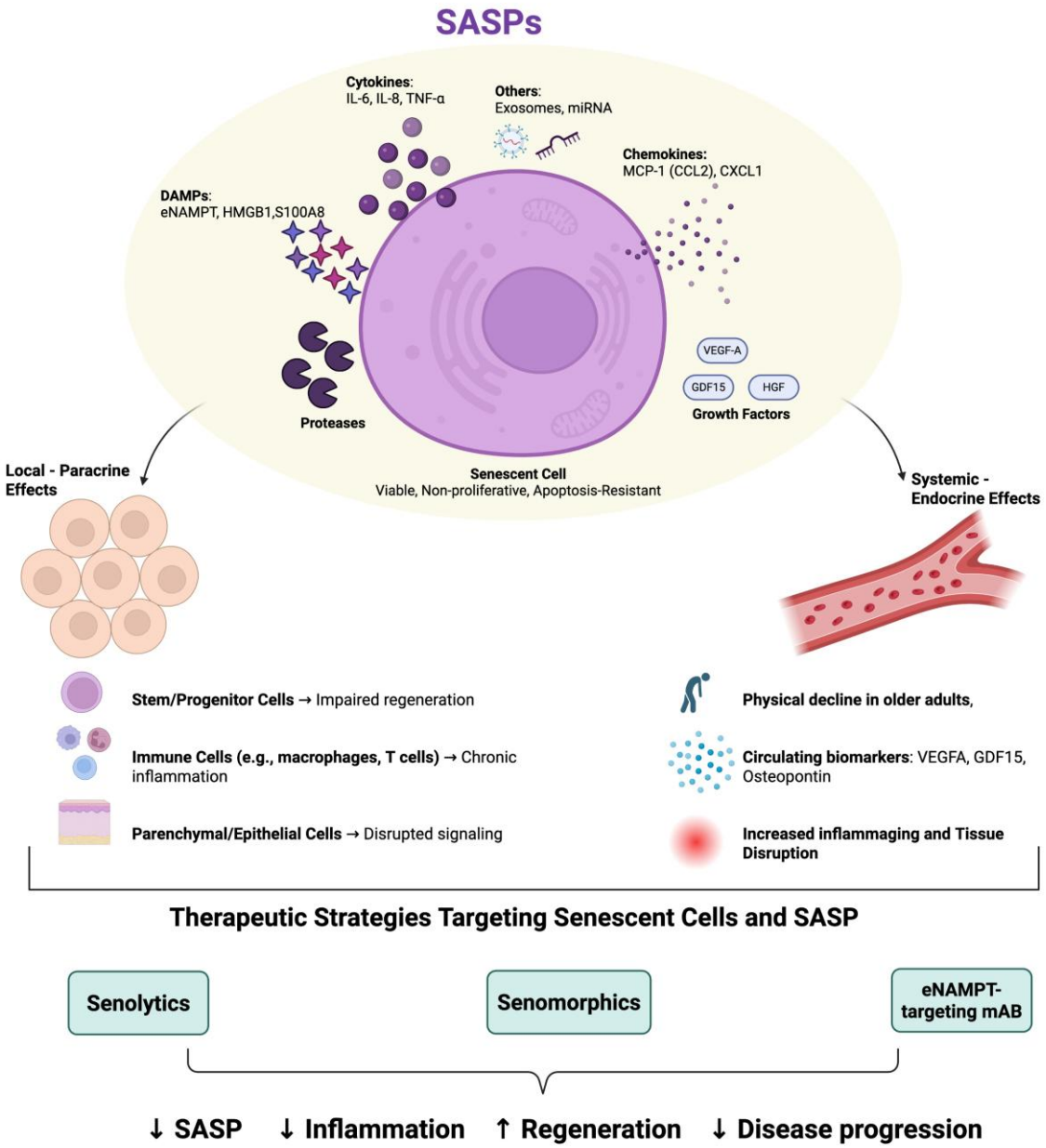


Figure 2. Systemic Effects of SASP and Therapeutic Modulation. Senescent cells adopt a proinflammatory phenotype characterized by the senescence-associated secretory phenotype (SASP), a complex and heterogeneous secretome composed of DAMPs, cytokines, chemokines, growth factors, proteases, and extracellular vesicle–associated signals such as exosomes and microRNAs. These factors act locally to disrupt tissue homeostasis by impairing regeneration, altering cell signaling, and remodeling the extracellular and vascular microenvironment, thereby promoting chronic inflammation. In parallel, SASP components can also enter systemic circulation and contribute to inflammaging and physical decline in older adults. Circulating SASP-associated factors therefore represent candidate biomarkers of biological aging and disease risk. Emerging senolytic therapies offer potential to mitigate these effects by clearing senescent cells.

The full contribution of age-related SASP induction across human tissues, however, remains poorly understood and warrants further investigation. Moreover, the heterogeneity of senescent cell populations across tissues, cell types, and disease contexts complicates efforts to define universal biomarkers or therapeutic targets and may partially explain the discrepancies across experimental systems and human studies findings. Understanding the cellular and molecular underpinnings of inflammaging offers a pathway to targeted interventions. The elimination of senescent cells using senolytic agents has shown promise in some murine models for preventing age-related pathology and improving tissue function [63]. The durability, safety, and translational relevance of these effects in humans, however, remain under study [64], perhaps due to the indiscriminate suppression of harmful and beneficial senescence. Therefore, identifying reliable biomarkers, such as circulating DAMPs, cytokines, or SASP components may help stratify individuals by inflammatory risk and tailor interventions accordingly (Fig. 2).

3.3. Remodeling of the Immune System and Inflammatory Biomarkers

Aging is accompanied by significant remodeling of the immune system potentially influenced by proinflammatory cytokines that are consistently elevated in older adults and strongly associated with chronic diseases, including cardiovascular disease, frailty, dementia, and all-cause mortality [65–69]. Emerging transcriptomic studies have revealed an increased expression of inflammatory genes, such as complement C1q A chain and β2-microglobulin, with advancing age and activation of these genes has been linked to heightened immune cell infiltration into various tissues [70]. Additional immune changes include an increase in monocytes and effector memory CD4+ T cells, alongside a decline in naïve T cells and plasmacytoid dendritic cells [71–73]. This broad, age-related decline of the entire immune system with a shift from a balanced immune landscape to a chronically-activated state, often termed "immunosenescence," impairs the body's ability to mount effective responses to new antigens while paradoxically promoting sustained, low-grade inflammation [1]. Immunosenescence can progress to a state of “immune exhaustion,” a related but distinct condition characterized by reversible T-cell dysfunction resulting from chronic antigenic stimulation [1]. Reduced thymic output, compromised hematopoietic stem cell function, and clonal expansion of senescent T cells further contribute to the decline in immune diversity and surveillance [74–76]. These age-associated immune alterations not only diminish host defense against infections and malignancies but also play a direct role in promoting tissue dysfunction and accelerating the onset of age-related pathologies [77]. Age-related immune remodeling, however, may not be uniformly detrimental, and the concept of immunosenescence is more nuanced than originally described. Recent vaccine trials [78, 79] demonstrate that older adults are capable of producing robust and clinically meaningful immune responses, particularly when modern adjuvants or optimized platforms effectively engage innate immune pathways. These findings suggest that immune aging involves compensatory adaptation rather than unidirectional loss of function. Consistent with this view, a recent high-resolution profiling study [80] shows that antigen-specific T cells in older adults exhibit preserved T-cell receptor diversity and gain innate-like transcriptional signatures without evidence of true senescence or exhaustion. These data emphasize that immune aging is heterogeneous across cell types and contexts, underscoring the need for more refined frameworks that distinguish detrimental dysfunction from adaptive remodeling. Collectively, these age-associated immune changes, encompassing both maladaptive inflammatory activation and preserved or compensatory immune capacities, form the complex biological foundation of inflammaging. This evolving understanding highlights the immune system as a critical target for interventions aimed at improving resilience, delaying disease onset, and promoting healthier aging, warranting continued investigation.

3.4. Sex Differences in Inflammaging

Inflammaging has distinct sex-specific trajectories, therefore, the integrated influence of biological sex, endocrine regulation, and different exposures across the lifespan can shape the etiology of inflammaging across sexes [81]. Females generally have more robust innate and adaptive immune responses than males. This is characterized by increased innate detection by pattern recognition receptors, higher expression of Toll-like receptors (specifically TLR-7), higher levels of interferon-α production, higher counts of $CD4^+$ T cells, more efficient antigen presenting cells and higher phagocytic activity in macrophages and neutrophils but lower numbers of natural killer cells [82, 83]. These differences could be partially attributed to the fact that several innate immunity genes have androgen response elements and estrogen response elements in their promoters and thus their expression can be affected by hormones [84]. While these enhanced immune responses provide women with increased resistance to infections and better vaccine responsiveness, they also render them

at a higher risk of chronic inflammation, immune reactivity, and autoimmune conditions [85–87]. At the molecular level, sex hormones play a critical role in immune signaling and immunometabolism. For example, estrogen can suppress NF-κB-mediated proinflammatory transcription, modulate macrophages polarization, and enhance mitochondrial oxidative capacity which is critical in immune cells [88–91]. Testosterone and androgens in males, on the other hand, enhance the expression of peroxisome proliferator-activated receptor-α (PPARα) in T cells, thereby suppressing inflammatory gene expression, and promoting fatty acid oxidation, lowering intracellular lipid accumulation, reducing ROS production and the generation of pro-inflammatory lipid species, thus limiting endoplasmic reticulum-stress induced inflammatory signaling [92–94].

The sudden drop in estrogen levels after menopause represents a critical inflection point in inflammaging trajectories in women [95, 96]. Also, menopause is often associated with redistribution of adiposity toward visceral depots, impaired mitochondrial function, and increased production of proinflammatory cytokines, such as IL-6, TNF-α, and C-reactive protein (CRP) [97–100]. These changes are often accompanied by altered immune cell composition, including an increase in the population of proinflammatory monocytes, a decrease in $CD4^+$ T and B lymphocytes, and heightened activation of innate immune pathways, all of which increase levels of systemic inflammation post-menopause [101–103]. In contrast, aging in men is characterized by a more gradual decline in androgen levels, with downstream effects on immune remodeling. This includes altered macrophage and T-cell function, as well as increased cardiometabolic inflammation, resulting in distinct patterns of immunosenescence that tend to favor chronic low-grade inflammatory activation rather than autoimmunity [104–107].

In addition to physiological sex-associated differences, sex-specific differences in lifestyle, nutrition, physical activity, environmental exposures, psychosocial stress, caregiving roles, and access to healthcare further modulate inflammation associated with aging (inflammaging) [81]. The combined influence of these factors produces heterogeneous inflammaging phenotypes that can differ in timing, magnitude, and tissue distribution between women and men. Collectively, this evidence underscores the necessity of sex- and life-stage-specific biomarker frameworks and precision approaches that account for sex-specific immune set points, hormonal transitions, particularly during menopause, and sex-associated differences in behavioral and environmental exposures when defining inflammaging phenotypes, interpreting inflammatory biomarkers, and tailoring interventions aimed at promoting healthy aging.

3.5. Modifiable Lifestyle and Environmental Factors

The severity of inflammaging is strongly modulated by lifestyle and environmental exposures **(**Fig. 3**)**. Poor nutrition, sedentary behavior, insufficient sleep, and chronic psychological stress are all known to increase inflammatory burden. Specifically, epidemiological studies have shown that adherence to anti-inflammatory dietary patterns, such as the Mediterranean diet, is associated with lower circulating levels of pro-inflammatory cytokines and a reduced risk of frailty, cardiovascular disease, and cognitive decline in older adults [108, 109]. Similarly, regular physical activity has consistently been associated with lower systemic inflammation, improved immune regulation, and delayed onset of age-related disease [110]. Good sleep quality has also been identified as a critical factor in modulating inflammation: both short and fragmented sleep are linked with elevated levels of IL-6 and CRP, as well as increased risk for metabolic syndrome and all-cause mortality in older individuals [111]. Social and psychosocial factors, including isolation, low socioeconomic status, and chronic psychological stress increase biomarkers of inflammation and plausibly affect the course of inflammaging [112, 113]. Longitudinal cohort studies have demonstrated that individuals with higher socioeconomic status tend to have lower levels of inflammatory markers and better aging trajectories [114, 115]. Finally, environmental exposures, such as air pollution, gut dysbiosis, and chronic infections (e.g., cytomegalovirus CMV), further exacerbate immune dysregulation [116–118]. Highlighting the contextual role of the environment, individuals living in areas of poor air quality [119] or exposed to extreme climates exhibited accelerated inflammatory aging and elevated disease risk [120]. Together, these findings underscore the role of lifestyle and environmental factors in driving inflammaging and identify potential biomarkers and molecular pathways for early detection and therapeutic intervention.

4. Clinical implications of inflammaging

Inflammaging is driven by intrinsic biological changes and genetic susceptibility [5], where genetic polymorphisms, particularly in DAMP- and cytokine-encoding genes, can alter inflammatory responses and increase susceptibility to conditions, such as cardiovascular disease, neurodegeneration, and certain cancers [121–123] as well as increased autoimmunity and higher cancer risk [124, 125]. Building on this genetic and

molecular foundation, the clinical consequences of inflammaging are broad and well-documented, reflecting its systemic impact on nearly every organ system and its diverse clinical manifestations.

Moreover, inflammaging can alter drug metabolism through its effects on the function of the liver and other organs and inflammatory signaling pathways, where age-related changes in pharmacokinetics and pharmacodynamics often necessitate careful adjustment of treatments to avoid adverse drug reactions or therapeutic failure in older patients [126]. In the following section, we explore the specific clinical manifestations and disease states linked to inflammaging, highlighting its role as a common underlying mechanism in age-related pathology.

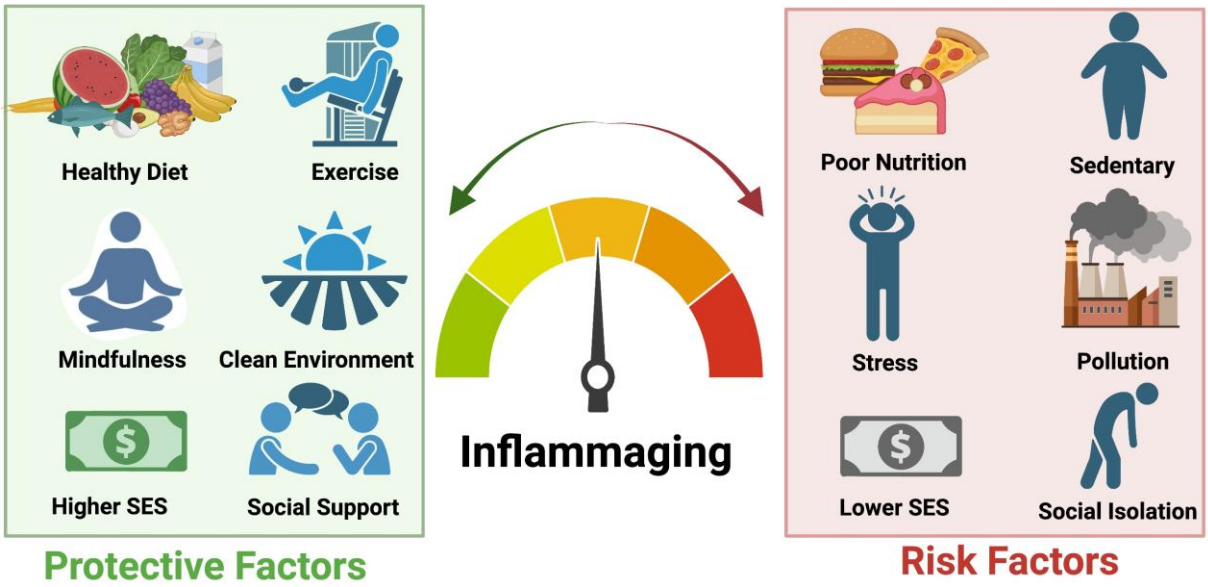


Figure 3. Lifestyle and Environmental Modulators of Inflammaging. The balance between protective and risk factors across the lifespan plays a critical role in shaping the trajectory of inflammaging. Protective factors, such as a healthy diet, regular physical activity, social support, mindfulness, clean environments, and higher socioeconomic status (SES), help mitigate systemic inflammation. In contrast, poor nutrition, sedentary behavior, chronic stress, pollution exposure, social isolation, and lower SES contribute to an elevated inflammatory burden. Modulating these factors may offer effective strategies to delay or reduce inflammaging and its associated health consequences.

4.1. Inflammaging and the Development of Frailty

A growing body of evidence links chronic low-grade inflammation to frailty in older adults, with elevated inflammatory markers strongly associated with physical and cognitive decline [127–129]. Frail older adults consistently exhibit elevated levels of inflammatory biomarkers, which are strongly associated with impaired mobility, sarcopenia, cognitive decline, and multimorbidity [5, 130]. Numerous studies have identified increased concentrations of IL-6, TNF-α, and C-X-C motif chemokine ligand 10 (CXCL10) in the serum of frail older adults, suggesting an association with frailty [128, 131–133]. Searle et al. described an association between inflammaging and frailty [134, 135], (measured by frailty index), and proinflammatory markers which are independently associated with chronological age and dichotomized frailty index [136]. In a larger study of over 400 home-dwelling older adults, Balsrud et al. [135] found that circulating levels of IL-6, cathepsin S, cystatin C, and glycoprotein acetyls-acetyls were positively associated with a frailty index [136] irrespective of chronological age and BMI. These findings indicated that inflammaging is not just a byproduct of aging but a driver of physiological decline.

Recent research has also explored how interventions targeting inflammation can influence frailty outcomes. A systematic review of intervention studies that improved frailty scores reported that exercise programs and dietary supplementation were associated with favorable changes in inflammatory markers, including increased IL-10 and reductions in IL-6, TNF-α, and CRP [137]. In a study of frail individuals aged 75 and older, Caldo-Silva et al. [138] found that a 40-week multifactorial intervention (combining multicomponent exercise with branched-chain amino acid supplementation) significantly improved frailty scores and simultaneously decreased plasma TNF-α levels. Therefore, targeting inflammatory pathways represents a potential strategy to prevent or ameliorate frailty. Larger randomized clinical trials are

needed, however, to fully evaluate the therapeutic potential of lifestyle, nutritional, and pharmacologic interventions in mitigating frailty and improving resilience in older adults.

While these associations are robust across studies, it is important to acknowledge that frailty itself remains a debated construct, with its prevalence and clinical characterization varying depending on whether a phenotype-based, deficit-accumulation, or mixed model is applied, thus affecting how inflammation-frailty relationships are interpreted. In recognition of these limitations, the gerontology field has increasingly embraced the concept of intrinsic capacity, which focuses on the composite of physical and cognitive abilities an individual can maintain rather than deficits alone [139]. Intrinsic capacity may provide a more precise framework for evaluating how chronic inflammation shapes functional aging and resilience.

4.2. Role of Inflammaging in Age-Related Diseases

Although many chronic diseases associated with aging, such as atherosclerosis, neuroinflammation, and cancer, begin to develop decades before older adulthood, their later-life expression and rate of progression are strongly shaped by age-related changes in immune regulation. Although early-life pathogenic processes may establish the initial disease trajectory, chronic low-grade inflammation with aging can amplify and accelerate these processes. Inflammaging can be considered a late-life "disease accelerator." In the sections below, we describe the contribution of inflammaging to the progression of multiple age-related conditions (Fig. 4), including musculoskeletal disease (sarcopenia), neurodegeneration, cardiovascular disease (evidence presented below), malignancy, metabolic dysfunction, and chronic liver disease (evidence presented in Appendix 1, and summarized in Supplementary Table 1).

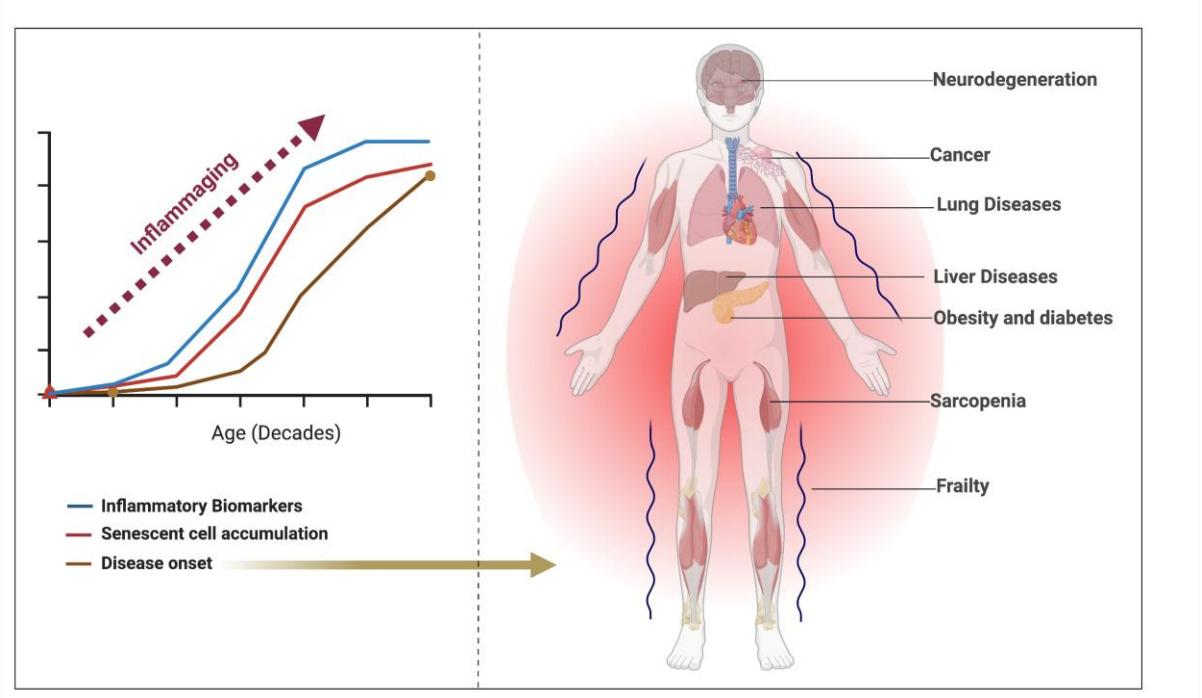


Figure 4. The trajectory of inflammaging and its systemic impact on aging-related diseases. With advancing age, there is a progressive increase in inflammatory biomarkers and senescent cell burden, contributing to a state of chronic low-grade inflammation termed "inflammaging". This biological process precedes and promotes the onset of various age-related diseases, including neurodegeneration, worsening of age-related lung diseases (COPD and idiopathic pulmonary fibrosis), cancer, liver disease, metabolic disorders (obesity and type 2 diabetes), sarcopenia, and frailty. The left panel illustrates how inflammaging correlates with biomarker accumulation and disease onset over time, while the right panel highlights the major organ systems affected.

4.2.a - Sarcopenia:

Although sarcopenia is multifactorial in origin, inflammaging is increasingly recognized as a major driver of muscle loss and physical function decline in older adults. Individuals with sarcopenia or impaired physical function consistently exhibit elevated circulating proinflammatory markers, such as IL-6, TNF-α and CRP [57, 137, 140, 141], supporting a mechanistic link between chronic low-grade inflammation and muscle deterioration. Over time, the age-associated low-grade inflammation promotes muscle catabolism, impairs

anabolic signaling, and interferes with mitochondrial and proteostatic functions, thereby accelerating the onset and progression of sarcopenia [142].

Elevated levels of proinflammatory markers, such as IL-6, TNF-α, and CRP, are associated with reduced mitochondrial function, activation of NF-κB signaling, and subsequent loss of lean muscle mass [143, 144] and are negatively associated with physical function [145]. Inflammaging also promotes the accumulation of senescent cells within skeletal muscle, further disrupting tissue homeostasis and repair mechanisms [146]. Collectively, these changes impair muscle metabolism, repair, and regeneration, ultimately exacerbating muscle wasting.

While inflammatory markers are often elevated in sarcopenic individuals, their predictive value varies. Fielding et al. [57] identified a panel of circulating markers, including activin A, Intercellular Adhesion Molecule 1 (ICAM1), Matrix Metalloproteinase 7 (MMP7), VEGFA, Tumor Necrosis Factor Receptor 1 (TNFR1), GDF15, IL-6, and eotaxin, that were predictive of mobility disability in a cohort of over 1,300 older adults.

Importantly, intervention studies have shown that targeting inflammation can improve sarcopenia outcomes. A meta-analysis of clinical trials found that improvements in sarcopenia following exercise and nutritional interventions were associated with reductions in IL-6 and CRP levels, supporting their potential utility as biomarkers of treatment response [137]. However, the utility of using inflammatory markers to guide clinical care requires further investigation.

4.2.b - Neurodegenerative diseases:

Neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), are increasingly recognized as age-related conditions closely linked to inflammaging. One of the key mechanisms driving neuroinflammation is cellular senescence within the central nervous system, particularly in astrocytes, microglia, and pericytes [147]. Senescent astrocytes and microglia adopt a proinflammatory phenotype, releasing components of SASP, while senescence in pericytes contributes to disruption of the blood-brain barrier, facilitating neuroinflammatory signaling and tissue damage [148]. In AD, aged microglia exhibit reduced capacity for clearing amyloid-beta (Aβ) fibrils, alongside increased secretion of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, contributing to Aβ plaque accumulation, oxidative stress, and neuronal loss [131, 149, 150]. Similarly, PD pathology involves chronic activation of senescent microglia, which release ROS, IL-6, TNF-α, and IFN-γ, molecules that exacerbate dopaminergic neuronal death in the substantia nigra [151–153]. Several studies have also reported elevated levels of circulating SASP-related proinflammatory markers in individuals with cognitive decline, AD, and PD, reinforcing the systemic nature of neuroinflammation in aging [154–157]. Collectively, these findings underscore the critical role of inflammaging and cellular senescence in neurodegeneration, highlighting the need for continued exploration of senescence-targeted therapies to preserve cognitive health in aging populations.

4.2.c - Cardiovascular diseases:

Numerous studies have shown that inflammaging is a major risk factor for cardiovascular disease (CVD) primarily through its contribution to atherosclerosis and chronic vascular inflammation [131, 137, 158]. In advanced stages of atherosclerosis, senescent cells accumulate within arterial plaques, creating a proinflammatory microenvironment that promotes extracellular matrix degradation, necrosis of the plaque core, and ultimately plaque rupture and acute vascular events [5, 147, 159, 160]. These unstable plaques are characterized by elevated expression of senescence markers, such as p16, $p14^{ARF}$, and multiple matrix metalloproteinases (MMPs), that further destabilize the arterial wall [5].

Systemic inflammation also plays a significant role in myocardial dysfunction and heart failure. Patients with myocardial dysfunction and heart failure commonly exhibit elevated plasma levels of TNF-α, IL-6, IL-1β, and eNAMPT (extracellular nicotinamide phosphoribosyl transferase), with these cytokines and DAMPs serving as independent predictors of both short- and long-term cardiovascular disease [131, 147]. Genetic evidence further underscores the link between inflammation and CVD risk where interestingly, patients with polymorphisms associated with lower levels of circulating IL-6 have a lower lifetime risk of cardiovascular disease [161, 162]. Therapeutically, targeting inflammation has shown promise in improving cardiovascular outcomes. In the CANTOS trial, canakinumab, a human monoclonal anti-IL-1β antibody, reduced recurrent cardiovascular events in more than 10,000 post-myocardial infarction patients with residual inflammation [163]. Similarly, the LoDoCo2 trial found that colchicine, an anti-inflammatory agent with broad cellular effects, reduced the risk of cardiovascular death, myocardial infarction, ischemic stroke, and coronary revascularization [164].

5. Precision medicine & targeted interventions in inflammaging

5.1. The Need for Precision Approaches

Since inflammaging is a heterogeneous process that varies significantly between individuals, precision medicine approaches are critical for identifying and treating individuals at elevated risk for inflammation-driven conditions. A variety of tools including multi-omic profiling (e.g., genomics, proteomics, metabolomics), biomarker panels, and advanced computational platforms leveraging artificial intelligence (AI) now offer the capability to stratify patients by unique inflammatory signatures and biological aging markers. These approaches allow for the identification of molecular endophenotypes of aging-related inflammation, improving risk prediction for diseases. AI-based models have also been applied to predict frailty risk, identify inflammaging subtypes, and detect early signals of sarcopenia or cognitive decline by integrating omics, clinical, and wearable data, highlighting their potential for real-time risk profiling and targeted interventions. For example, integrated omics approaches have revealed distinct immune aging trajectories among older adults, highlighting specific transcriptional and metabolic signatures associated with chronic low-grade inflammation [165, 166].

Longitudinal studies using plasma proteomics have shown that a biomarker signature of aging can predict both health outcomes and lifespan, providing a molecular readout that surpasses chronological age in forecasting functional decline [167, 168]. In a large-scale study, Tanaka et al. [167] identified a 6-protein proteomic age signature, which predicted the accumulation of chronic diseases and all-cause mortality. Additionally, He et al. [168] used single-cell RNA sequencing to identify differentially expressed SASP-related genes between an older and young group. They reported that the level of *IGFBP7* expressed in the older group was higher than that of the younger group, showing that IGFBP7 may be a biomarker of aging. Similarly, single-cell transcriptomic analyses of human testicular tissue have identified senescence-associated secretory phenotype (SASP) features linked to tissue-specific aging, offering insight into how cellular senescence contributes to organ dysfunction over time. Collectively, these findings demonstrate that multi-omic profiling can uncover individual-specific inflammatory and senescence signatures, laying the groundwork for personalized interventions aimed at mitigating age-associated morbidity and promoting healthy aging.

To potentially enhance the translational clarity, a preliminary tiered biomarker framework for inflammaging can be conceptualized, recognizing that to date, no consensus diagnostic criteria currently exist. Inflammaging would likely be best captured through a multi-domain approach integrating systemic inflammatory biomarkers (e.g., CRP, IL-6), mechanistic and/or tissue-related markers reflecting upstream pathways, and multi-omic signatures integrating transcriptomic, proteomic and/or metabolomic analyses. These layers can be integrated and optimized by computational approaches, such as machine learning, to identify inflammaging endotypes, predict disease trajectories and inform precision interventions (Fig. 5).

5.2. Artificial Intelligence and Predictive Modeling

Artificial intelligence, particularly machine learning (ML), is emerging as a powerful tool to integrate complex biological datasets and improve risk prediction. These models integrate multimodal data streams, including genomics, proteomics, metabolomics, clinical biomarkers, and lifestyle factors, to reveal latent inflammatory trajectories that are not captured by traditional analyses. Artificial intelligence, specifically, can potentially uncover early indicators of inflammaging, model disease trajectories, and enable the personalization of therapeutic strategies. For instance, Schafer et al. [169] utilized a gradient boosting machine (GBM) model with a panel of seven SASP proteins (GDF15, FAS, OPN, TNFR1, activin A, CCL3, IL-15) to predict adverse outcomes in older adults undergoing major surgery, outperforming models based on age or single biomarkers alone. Unlike conventional regression-based methods, ML models can capture high-order, nonlinear interactions among biological and behavioral features, improving sensitivity for complex aging-related patterns. Similarly, the study by Fielding et al. [57] described above, evaluated over 1,300 older adults and used a GBM model to identify the SASP biomarker panel associated with major mobility disability. The same model also identified top covariates (e.g., MPO, ICAM1, OPN, IL-15, GDF15, VEGFA) that predicted functional decline based on short physical performance battery scores over 6 months.

Of note, the above-mentioned predictive models were evaluated using established performance metrics, including area under the receiver operating characteristic curve (AUROC), calibration indices, and cross-validation strategies to assess internal robustness [170]. Cross-validation techniques, such as k-fold resampling, serve to mitigate optimistic bias during model development, particularly in moderate-sized aging cohorts. However, internal validation alone does not ensure transportability [171]. External validation across independent and demographically distinct populations remains a critical challenge in inflammaging research, as models trained in relatively homogeneous cohorts may exhibit reduced performance when applied to more diverse aging populations. Furthermore, high-dimensional omics datasets introduce substantial risk of overfitting [172], especially when feature counts far exceed sample size.

Regularization techniques, feature selection methods, and dimensionality reduction approaches [173] are therefore essential to improve generalizability and prevent spurious biomarker identification.

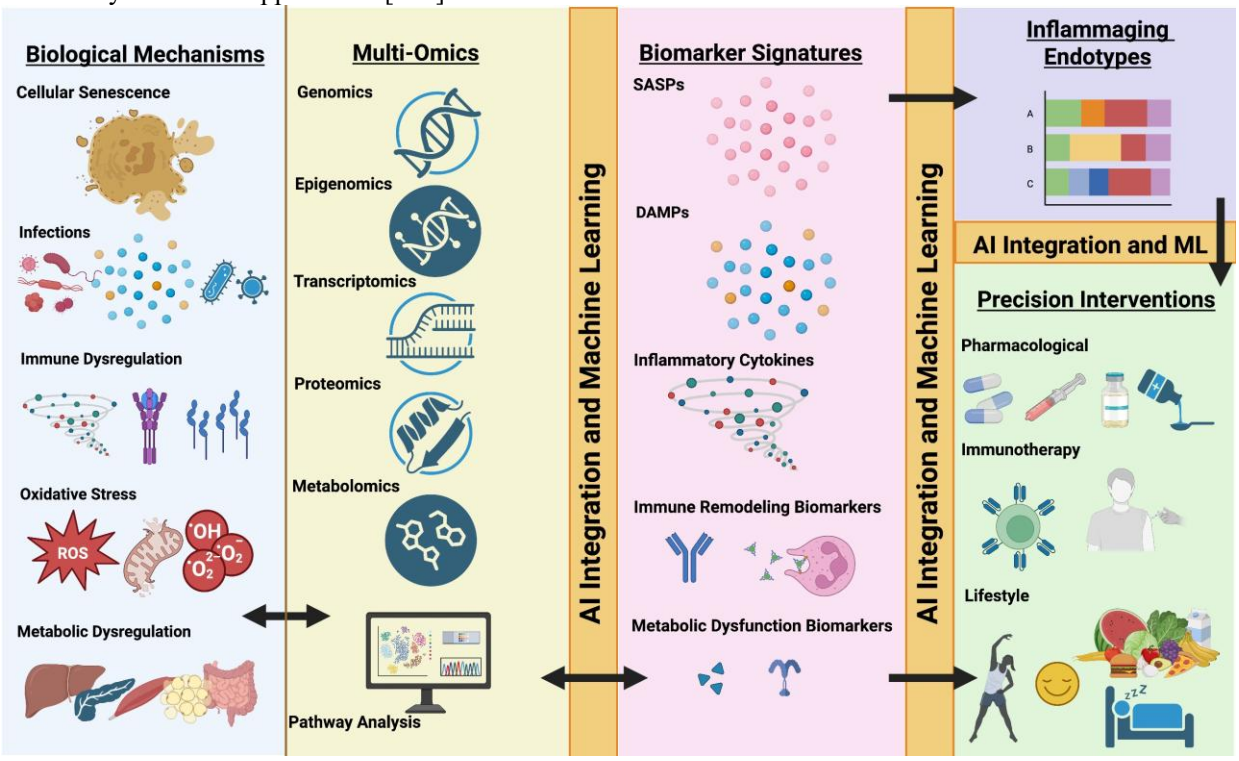


Figure 5. Translational framework linking biological mechanisms of inflammaging to biomarker discovery, AI-based stratification, and precision interventions. Age-related biological processes including cellular senescence, chronic infections, immune dysregulation, oxidative stress, and metabolic dysfunction contribute to persistent low-grade inflammation characteristic of inflammaging. Multi-omic profiling approaches (genomics, epigenomics, transcriptomics, proteomics, and metabolomics) with the help of ML, enable the identification of molecular pathways and biomarker signatures, including SASP components, DAMPs, inflammatory cytokines and biomarkers of immune remodeling and metabolic dysregulation. Integration of these multidimensional datasets using artificial intelligence and ML approaches allows classification of individuals into distinct inflammaging endotypes, reflecting heterogeneous biological aging trajectories. These endotypes, also with the help of ML, can inform precision interventions, including pharmacologic therapies, immunomodulatory approaches, and lifestyle strategies aimed at reducing inflammatory burden and improving health-span.

Artificial intelligence also provides tools to personalize treatment for each patient. By establishing inflammaging endotypes based on biomarker clusters and multi-omic data, there is potential for algorithm-guided personalized therapy, such as recommending an anti-inflammatory diet for individuals with mildly elevated systemic inflammatory markers or using senolytic treatments for those exhibiting a high SASP phenotype. A growing number of studies have already begun using ML to sort subgroupings of patients, showing promising results for the future of personalized treatments [174, 175]. For example, MacEachern et al.[175] describe how ML models can be applied to stratify patients based on genotypic and phenotypic features, enabling subgroup classification that may guide differential therapeutic strategies. Such stratification could allow clinicians to assign anti-inflammatory or senolytic treatments selectively to those individuals whose molecular signatures indicate elevated inflammaging, potentially improving therapeutic precision. These studies highlight the translational value of AI-based approaches in identifying high-risk individuals and optimizing clinical decision-making.

Equally important, explainable AI (XAI) frameworks, such as SHAP (SHapley Additive exPlanations) or feature attribution analyses, now enable interpretation of model outputs by identifying which biomarkers or pathways most strongly drive predictions [176]. This interpretability strengthens biological insight, enhances clinician trust, and guides hypothesis generation for targeted interventions. At the same time, ethical considerations related to fairness, bias, and equity are particularly salient in aging research, as AI models trained on non-representative cohorts may systematically underperform across sex, race, or socioeconomic groups. However, challenges remain regarding generalizability, data harmonization, and population diversity. Models trained on homogeneous datasets may not perform

consistently across settings, underscoring the need for representative data and bias mitigation strategies in inflammaging research. Rigorous model validation using diverse, longitudinal datasets is essential to ensure robustness, clinical relevance, and reproducibility of AI-generated predictions across aging populations. Without such validation, models risk propagating bias, misclassification, or inequitable performance, ultimately undermining both scientific validity and ethical deployment in heterogeneous aging populations. To advance both fairness and data privacy, federated or privacy-preserving AI frameworks have emerged as promising approaches for large-scale inflammaging research. These methods enable model training across institutions without direct data sharing [177], reducing the risk for re-identification while maintaining the diversity and representativeness needed for equitable, generalizable predictions. Such approaches can accelerate discovery while maintaining participant privacy and regulatory compliance.

5.3. Targeted Therapies and Interventions

Multiple therapeutic strategies are being explored to counteract inflammaging including biologic therapies, senolytics, senomorphics (see Box 1 for definition), and anti-inflammatory agents. Likely, a broad range of holistic, multi-domain interventions will be needed to address the many sources of age-related inflammatory burden. In addition to pharmacologic approaches, lifestyle choices and environmental modifications play critical roles in modulating systemic inflammatory tone across the lifespan.

Box 1. Senolytics vs. senomorphics.

Senolytics are agents that selectively eliminate senescent cells by inducing apoptosis, thereby reducing senescent cell burden and associated inflammatory signaling. While effective in preclinical models, their use raises concerns about off-target toxicity and the unintended removal of senescent cells with beneficial roles in tissue repair or tumor suppression.

Senomorphics suppress the senescence-associated secretory phenotype (SASP) without killing senescent cells, aiming to reduce inflammation while preserving tissue structure. These agents typically require chronic administration and may offer a safer approach in contexts where senescent cell clearance could be harmful.

Key difference: Senolytics remove senescent cells; senomorphics modulate their inflammatory behavior.

5.3.1. Pharmaceutical therapies

As an example of DAMP- or cytokine-targeting biologic therapies, eNAMPT, a secreted component of the SASP, has emerged as a promising therapeutic target. Preclinical studies indicate that a humanized eNAMPT-neutralizing monoclonal antibody currently in Phase 2 clinical trials in Acute Respiratory Distress Syndrome (ARDS) mitigates pathological inflammatory tissue damage, traumatic brain injury, autoimmune disorders, organ fibrosis (e.g., lung, cardiac, hepatic, colon, as well as progression of prostate and breast cancer [156, 178–181]. Ongoing studies designed to clarify the contribution of this upstream DAMP to inflammaging pathobiology and frailty offer the potential for a novel approach to modulate inflammatory, fibrotic and neoplastic pathways associated with senescence. Certain therapies have been applied in a particular context, such as targeting fat tissues. While extensive preclinical data have demonstrated the efficacy of senolytic therapies in reducing senescent adipocyte progenitors, clinical translation remains limited [182]. Notably, an open-label Phase I pilot study using Dasatinib and Quercetin (D+Q) in patients with diabetic kidney disease showed a reduction in senescent cell burden in adipose tissue, as well as decreased levels of circulating SASP factors such as IL-1α, IL-6, MMP-9, and MMP-12 [183]. While this trial holds promise for the use of senolytic therapies in metabolic syndrome, larger and longer-term clinical trials are needed to fully assess the efficacy and safety of senolytic interventions in obesity and T2DM.

Despite promising preclinical data, therapeutic targeting of senescent cells and SASP pathways remains an area of active debate. Potential off-target toxicity, impaired tissue repair capacity, immune dysregulation, and the possibility of eliminating beneficial senescent populations required for physiological remodeling or tumor suppression, remain a concern [184–186]. In addition, most efficacy data derived from short-term animal studies and long-term safety, optimal dosing strategies, and patient selection criteria in humans remain largely undefined.

Senomorphics are small molecules that act to suppress some or all senescent cell activity, functioning as SASP inhibitors and lowering the level of cellular stress without killing the cell [187]. In contrast to senolytics,

which are effective in a short-term intermittent manner, senomorphics do not eliminate senescent cells and thus must be administered chronically for an extended timeframe [188]. Chronic administration raises additional concerns regarding cumulative toxicity, incomplete suppression of deleterious SASP signaling, and the potential for adaptive resistance mechanisms, underscoring the need for careful longitudinal evaluation. As for immunotherapies and vaccines, novel approaches, such as senescence-targeted vaccines and immune cell-based therapies, are under development to enhance the clearance of harmful senescent cells [189]. For example, chimeric antigen receptor (CAR)-T cells engineered against senescence-specific antigens like urokinase plasminogen activator receptor (uPAR), and NKG2D ligand, have successfully eliminated senescent cells *in vivo*, reversing age-related tissue dysfunction in mice and non-human primates [190–192]. Additionally, senolytic vaccines, such as those targeting GPNMB and CD153, have been shown to induce antibody-mediated clearance of senescent cells, improving metabolic health in preclinical models [193]. While these immunotherapeutic approaches demonstrate impressive efficacy in preclinical systems, their translational applicability is uncertain. This is due to the complexity of senescent antigen heterogeneity, potential immune-related adverse events, and challenges in achieving selective targeting without collateral tissue injury. Thus, human safety and feasibility data remain limited.

5.3.2. Non-pharmacological Interventions

Several non-pharmacologic interventions have demonstrated senomorphic effects, modulating SASP without killing senescent cells. Nutritional interventions and exercise have both been shown to exert senomorphic effects by suppressing SASP factors and improving mitochondrial function [194]. For example, Landberg et al. [195] demonstrated that flavonoid-rich diets are associated with lower concentrations of inflammatory biomarkers. Longitudinal studies demonstrated that adopting a low-glycemic index diet combined with regular resistance training significantly improved insulin sensitivity in individuals with T2DM [196, 197]. These improvements are highly relevant to inflammaging, as both insulin resistance and metabolic dysfunction are strongly linked to chronic low-grade inflammation associated with aging [198].

Various nutrients, such as omega-3 fatty acids and polyphenols, have been shown to have anti-inflammatory properties which may help reduce age-related inflammation [187, 199]. An increase in consumption of these nutrients through practical dietary patterns, such as the Mediterranean diet or a plant-forward diet, may be viable adjunctive strategies to reduce the inflammaging burden. For example, Tyrovolas et al. [200] conducted a study on the effect of the Mediterranean diet on older adults aged 65 and above and found high nutritional anti-inflammatory scores were associated with successful aging. Additionally, they reported that participants with higher proinflammatory nutrition scores had a higher prevalence of hypercholesterolemia and lower levels of successful aging. Enhancing metabolic health through dietary modifications may indirectly attenuate systemic inflammatory burden.

Holistic strategies that address multiple drivers of inflammaging, including physical activity, nutrition, stress-reduction practices, social connectedness, and cognitive engagement, may provide broad benefits. Unlike pharmacologic agents that target single pathways, these approaches modulate interconnected biological, behavioral, and environmental factors contributing to chronic inflammation. As such, integrating exercise, nutritional strategies, and senolytic therapies altogether, may therefore provide a personalized and synergistic approach in counteracting inflammaging and its downstream consequences. Potentially, the safest approach would be by starting with low-risk lifestyle changes before escalating to targeted pharmacology where appropriate. However, long-term clinical trials in humans are still needed to determine the safety, sustainability, and long-term effectiveness of these combined strategies in aging populations.

Ultimately, precision algorithms that integrate behavioral, biological, and contextual data can guide the development of targeted immunomodulatory therapies and personalized lifestyle modifications. For instance, individuals with metabolic syndrome and evidence of insulin resistance may benefit from dietary strategies that enhance mitochondrial efficiency and improve glucose handling, such as time-restricted eating or exercise programs designed to increase insulin sensitivity [201–203]. In contrast, those with immune dysfunction or markers of chronic inflammation may require interventions aimed at restoring immune balance, including senolytic or anti-inflammatory therapies to reduce the burden of senescent cells and modulate cytokine signaling [204–206]. By tailoring interventions to an individual's biological endotype, this convergence of AI and precision medicine holds promise for mitigating inflammaging, extending lifespan, improving functional outcomes, and reducing the burden of chronic disease in aging populations. Future integration of these AI-derived inflammaging risk profiles into clinical decision-support systems could enable proactive, personalized management of aging trajectories at the point of care.

6. Conclusions

Unlike prior inflammaging reviews that primarily catalog molecular mechanisms or disease associations, this review advances the field by integrating a multilayer biomarker framework with emerging AI-based risk stratification approaches and a clinically oriented intervention roadmap. By explicitly distinguishing adaptive from maladaptive inflammation and situating inflammaging within precision-medicine paradigms, we provide a translational scaffold that bridges biology, data science, and clinical decision-making. This synthesis positions inflammaging not merely as a descriptive construct, but as a modifiable, measurable target for intervention. Future research in inflammaging should prioritize developing organ-specific biomarker panels and multi-modal indexes, integrating traditional plasma inflammatory markers with innovative extracellular vesicle-derived molecular signatures that capture tissue-specific immune and metabolic dysregulation.

Understanding and addressing inflammaging remains a daunting challenge due to the pathobiological, clinical, and methodological complexities involved. The heterogeneity of the aging population, spanning diverse genetic backgrounds, lifestyles, and comorbidities, complicates the identification of universal biomarkers and mechanistic pathways. Correspondingly, inflammaging evidently manifests in different individuals through distinct molecular endotypes defined by differential immune, metabolic, and senescence-associated signatures. Moreover, the multifactorial nature of inflammaging, influenced by environmental exposures, chronic infections, oxidative stress, and cellular senescence, makes it difficult to isolate specific contributors to age-related inflammation [46, 201–204], particularly given that some degree of inflammatory signaling remains necessary for tissue homeostasis and immune defense. Disentangling the effects of inflammaging from those of normal aging is challenging, but one key distinction is the transition from adaptive, transient inflammation to persistent, dysregulated inflammation with impaired resolution pathways. Ethical and logistical constraints in conducting long-term studies in older adults further complicate progress in this area.

Importantly, despite all these barriers, the clinical relevance of inflammaging is profound. It underlies the development and progression of multiple chronic diseases, including cardiovascular disease, sarcopenia, T2DM, cancer, and neurodegenerative disorders, and contributes significantly to multimorbidity, reduced functional independence, and increased healthcare costs [211–214]. Its impact on quality of life and long-term care needs in older adults is substantial, demanding proactive, system-level responses [215–217].

To overcome these challenges, a paradigm shift is needed, one that embraces interdisciplinary collaboration and advanced tools, such as ML and AI. These technologies can help unravel the complexity of inflammaging, identify different endotypes and personalized risk profiles, and guide the development of context and time-specific precision-based strategies to delay or mitigate age-related functional decline and diseases. Continued investment in innovative tools to assess inflammaging, especially those that are time- and cost-efficient, will be critical for translating basic science discoveries into real-world clinical solutions. Moving forward, greater emphasis should be placed on human studies, particularly longitudinal and tissue-specific investigations, to better characterize inflammaging phenotypes and their clinical consequences. Understanding the intricacies of inflammaging is crucial for developing strategies to mitigate its detrimental effects on aging and improve clinical outcomes in older adults. Ultimately, tailoring healthcare to account for the heterogeneity of inflammaging will pave the way for individualized therapeutic approaches rather than one-size-fits-all strategies, leading to improved health span, increased longevity, and a more active, independent aging population.

Competing interest

The authors declare no competing interests.

Authors' contributions

RSZ: Conceptualization, outlining, writing – original draft, writing – review & editing, figures. AS, AP, JG, LP: Writing – original draft; writing – review & editing. SA: Outlining, writing – review & editing. SR, PV, CL: Writing – review & editing.

Acknowledgments

1-Drs. Anton and Leeuwenburgh's efforts are supported by a grant from the National Institute on Aging (R01 AG075136), **2**-Dr. Zeidan's contribution is supported by a training grant from the National Institute on Aging (T32 AG062728) and by a pilot grant (AWD19470 / 90108 / R33AG071744), **3**-Dr. Shirali's contribution is supported by University of Florida Claude D. Pepper Older Americans Independence Center (P30AG028740) and the GEMSSTAR grant from the National Institute on Aging (R03AG095539), and **4**-Dr. Garcia's efforts are supported by R01 HL141387, and P01 HL126609.

The authors would like to acknowledge and apologize that not all the relevant literature has been cited due to space constraints. All authors have read and approved the

final version of this manuscript. Model figures were made using BioRender.com.

Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2025.1557.

References

[1] Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci, 908:244–254.

[2] Tan BL, Norhaizan ME (2021). Chronic Inflammation and Aging (Inflammaging). In: Tan BL, Norhaizan ME, editors Role Antioxid. Longev. Age-Relat. Dis. Cham: Springer International Publishing, 39–50.

[3] Teissier T, Boulanger E, Cox LS (2022). Interconnections between Inflammageing and Immunosenescence during Ageing. Cells, 11:359.

[4] Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. (2017). Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front Immunol, 8:1960.

[5] Ferrucci L, Fabbri E (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol, 15:505–522.

[6] Ajoolabady A, Pratico D, Tang D, Zhou S, Franceschi C, Ren J (2024). Immunosenescence and inflammaging: Mechanisms and role in diseases. Ageing Res Rev, 101:102540.

[7] Santoro A, Bientinesi E, Monti D (2021). Immunosenescence and inflammaging in the aging process: age-related diseases or longevity? Ageing Res Rev, 71:101422.

[8] Kovacs EJ, Boe DM, Boule LA, Curtis BJ (2017). Inflammaging and the Lung. Clin Geriatr Med, 33:459–471.

[9] Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A (2018). Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nat Rev Endocrinol, 14:576–590.

[10] Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. (2019). Chronic inflammation in the etiology of disease across the life span. Nat Med, 25:1822–1832.

[11] Calder PC, Bosco N, Bourdet-Sicard R, Capuron L, Delzenne N, Doré J, et al. (2017). Health relevance of the modification of low grade inflammation in ageing (inflammageing) and the role of nutrition. Ageing Res Rev, 40:95–119.

[12] Arai Y, Martin-Ruiz CM, Takayama M, Abe Y, Takebayashi T, Koyasu S, et al. (2015). Inflammation, But Not Telomere Length, Predicts Successful Ageing at Extreme Old Age: A Longitudinal Study of Semi-supercentenarians. EBioMedicine, 2:1549–1558.

[13] Li X, Li C, Zhang W, Wang Y, Qian P, Huang H (2023). Inflammation and aging: signaling pathways and intervention therapies. Signal Transduct Target Ther, 8:239.

[14] Wei S, Eksioglu EA, Chen X, Cluzeau T, Basiorka A, Burnette A, et al. (2015). Inflammaging-Associated Metabolic Alterations Foster Development of the MDS Genotype. Blood, 126:144.

[15] Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA (2018). Age and Age-Related Diseases: Role of Inflammation Triggers and Cytokines. Front Immunol, 9:586.

[16] Shive C, Pandiyan P (2022). Inflammation, Immune Senescence, and Dysregulated Immune Regulation in the Elderly. Front Aging, 3:840827.

[17] Huang W, Hickson LJ, Eirin A, Kirkland JL, Lerman LO (2022). Cellular senescence: the good, the bad and the unknown. Nat Rev Nephrol, 18:611–627.

[18] Nishimoto S, Fukuda D, Higashikuni Y, Tanaka K, Hirata Y, Murata C, et al. (2016). Obesity-induced DNA released from adipocytes stimulates chronic adipose tissue inflammation and insulin resistance. Sci Adv, 2:e1501332.

[19] Mancuso P, Bouchard B (2019). The Impact of Aging on Adipose Function and Adipokine Synthesis. Front Endocrinol, 10:137.

[20] Markovič R, Grubelnik V, Vošner HB, Kokol P, Završnik M, Janša K, et al. (2022). Age-Related Changes in Lipid and Glucose Levels Associated with Drug Use and Mortality: An Observational Study. J Pers Med, 12:280.

[21] Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9:7204–7218.

[22] Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, et al. (2020). Inflammation and cardiovascular disease: From mechanisms to therapeutics. Am J Prev Cardiol, 4:100130.

[23] Wang H, Jing Z-C (2020). Inflammation and cardiovascular diseases. Chronic Dis Transl Med, 6:215–218.

[24] Grivennikov SI, Greten FR, Karin M (2010). Immunity, inflammation, and cancer. Cell, 140:883–899.

[25] Petrescu M, Vlaicu SI, Ciumărnean L, Milaciu MV, Mărginean C, Florea M, et al. (2022). Chronic Inflammation-A Link between Nonalcoholic Fatty Liver Disease (NAFLD) and Dysfunctional Adipose Tissue. Med Kaunas Lith, 58:641.

[26] Rovina N, Koutsoukou A, Koulouris NG (2013). Inflammation and immune response in COPD: where do we stand? Mediators Inflamm, 2013:413735.

[27] Baer PC, Koch B, Geiger H (2020). Kidney Inflammation, Injury and Regeneration. Int J Mol Sci, 21:1164.

[28] Zhang W, Xiao D, Mao Q, Xia H (2023). Role of neuroinflammation in neurodegeneration development. Signal Transduct Target Ther, 8:267.

[29] Chitnis T, Weiner HL (2017). CNS inflammation and neurodegeneration. J Clin Invest, 127:3577–3587.

[30] Liberale L, Badimon L, Montecucco F, Lüscher TF, Libby P, Camici GG (2022). Inflammation, Aging, and

Cardiovascular Disease: JACC Review Topic of the Week. J Am Coll Cardiol, 79:837–847.
[31] Costantini E, D'Angelo C, Reale M (2018). The Role of Immunosenescence in Neurodegenerative Diseases. Mediators Inflamm, 2018:6039171.
[32] Ferrucci L, Fabbri E (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol, 15:505–522.
[33] Pahwa R, Goyal A, Jialal I (2025). Chronic Inflammation. StatPearls .
[34] Lee YS, Olefsky J (2021). Chronic tissue inflammation and metabolic disease. Genes Dev, 35:307–328.
[35] Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, et al. (2019). Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes. Front Physiol, 10:1607.
[36] Alexander M, Cho E, Gliozheni E, Salem Y, Cheung J, Ichii H (2024). Pathology of Diabetes-Induced Immune Dysfunction. Int J Mol Sci, 25:7105.
[37] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G (2013). The hallmarks of aging. Cell, 153:1194–1217.
[38] Singh A, Schurman SH, Bektas A, Kaileh M, Roy R, Wilson DM, et al. (2024). Aging and Inflammation. Cold Spring Harb Perspect Med, 14:a041197.
[39] Sanada F, Taniyama Y, Muratsu J, Otsu R, Shimizu H, Rakugi H, et al. (2018). Source of Chronic Inflammation in Aging. Front Cardiovasc Med, 5:12.
[40] Franceschi C, Capri M, Monti D, Giunta S, Olivieri F, Sevini F, et al. (2007). Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev, 128:92–105.
[41] García-Domínguez M (2025). Pathological and Inflammatory Consequences of Aging. Biomolecules, 15:404.
[42] Lu RJ, Wang EK, Benayoun BA (2022). Functional genomics of inflamm-aging and immunosenescence. Brief Funct Genomics, 21:43–55.
[43] Gadoth A, Ourfalian K, Basnet S, Kunzweiler C, Bohn RL, Fülöp T, et al. (2024). Potential relationship between cytomegalovirus and immunosenescence: Evidence from observational studies. Rev Med Virol, 34:e2560.
[44] Alberro A, Iribarren-Lopez A, Sáenz-Cuesta M, Matheu A, Vergara I, Otaegui D (2021). Inflammaging markers characteristic of advanced age show similar levels with frailty and dependency. Sci Rep, 11:4358.
[45] Franceschi C, Campisi J (2014). Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci, 69 Suppl 1:S4-9.
[46] Ferrucci L, Gonzalez-Freire M, Fabbri E, Simonsick E, Tanaka T, Moore Z, et al. (2020). Measuring biological aging in humans: A quest. Aging Cell, 19:e13080.
[47] Picca A, Faitg J, Auwerx J, Ferrucci L, D'Amico D (2023). Mitophagy in human health, ageing and disease. Nat Metab, 5:2047–2061.
[48] Franceschi C, Valensin S, Bonafè M, Paolisso G, Yashin AI, Monti D, et al. (2000). The network and the remodeling theories of aging: historical background and new perspectives. Exp Gerontol, 35:879–896.
[49] Kepp O, Galluzzi L, Kroemer G (2011). Mitochondrial control of the NLRP3 inflammasome. Nat Immunol, 12:199–200.
[50] Picca A, Lezza AMS, Leeuwenburgh C, Pesce V, Calvani R, Landi F, et al. (2017). Fueling Inflamm-Aging through Mitochondrial Dysfunction: Mechanisms and Molecular Targets. Int J Mol Sci, 18:933.
[51] Song S, Lam EW-F, Tchkonia T, Kirkland JL, Sun Y (2020). Senescent Cells: Emerging Targets for Human Aging and Age-Related Diseases. Trends Biochem Sci, 45:578–592.
[52] Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, et al. (2019). Cellular Senescence: Defining a Path Forward. Cell, 179:813–827.
[53] Coppé J-P, Desprez P-Y, Krtolica A, Campisi J (2010). The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu Rev Pathol, 5:99–118.
[54] Basisty N, Kale A, Jeon OH, Kuehnemann C, Payne T, Rao C, et al. (2020). A proteomic atlas of senescence-associated secretomes for aging biomarker development. PLoS Biol, 18:e3000599.
[55] Faget DV, Ren Q, Stewart SA (2019). Unmasking senescence: context-dependent effects of SASP in cancer. Nat Rev Cancer, 19:439–453.
[56] Steinmetz T, Schaadt M, Gähl R, Schenk V, Diehl V, Pfreundschuh M (1988). Phase I study of 24-hour continuous intravenous infusion of recombinant human tumor necrosis factor. J Biol Response Mod, 7:417–423.
[57] Fielding RA, Atkinson EJ, Aversa Z, White TA, Heeren AA, Achenbach SJ, et al. (2022). Associations between biomarkers of cellular senescence and physical function in humans: observations from the lifestyle interventions for elders (LIFE) study. GeroScience, 44:2757–2770.
[58] Fielding RA, Atkinson EJ, Aversa Z, White TA, Heeren AA, Mielke MM, et al. (2024). Biomarkers of Cellular Senescence Predict the Onset of Mobility Disability and Are Reduced by Physical Activity in Older Adults. J Gerontol A Biol Sci Med Sci, 79:glad257.
[59] Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, et al. (2014). An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell, 31:722–733.
[60] Campisi J (2001). Cellular senescence as a tumor-suppressor mechanism. Trends Cell Biol, 11:S27-31.
[61] Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, et al. (2008). Senescence of activated stellate cells limits liver fibrosis. Cell, 134:657–667.
[62] Muñoz-Espín D, Cañamero M, Maraver A, Gómez-López G, Contreras J, Murillo-Cuesta S, et al. (2013). Programmed cell senescence during mammalian embryonic development. Cell, 155:1104–1118.
[63] Xu M, Pirtskhalava T, Farr JN, Weigand BM, Palmer AK, Weivoda MM, et al. (2018). Senolytics Improve Physical Function and Increase Lifespan in Old Age. Nat Med, 24:1246–1256.
[64] Chaib S, Tchkonia T, Kirkland JL (2022). Cellular senescence and senolytics: the path to the clinic. Nat Med, 28:1556–1568.

[65] Parker D, Sloane R, Pieper CF, Hall KS, Kraus VB, Kraus WE, et al. (2019). Age-Related Adverse Inflammatory and Metabolic Changes Begin Early in Adulthood. J Gerontol A Biol Sci Med Sci, 74:283–289.

[66] Ridker PM, Stampfer MJ, Rifai N (2001). Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA, 285:2481–2485.

[67] Shen X-N, Niu L-D, Wang Y-J, Cao X-P, Liu Q, Tan L, et al. (2019). Inflammatory markers in Alzheimer's disease and mild cognitive impairment: a meta-analysis and systematic review of 170 studies. J Neurol Neurosurg Psychiatry, 90:590–598.

[68] Walker KA, Walston J, Gottesman RF, Kucharska-Newton A, Palta P, Windham BG (2019). Midlife Systemic Inflammation Is Associated With Frailty in Later Life: The ARIC Study. J Gerontol A Biol Sci Med Sci, 74:343–349.

[69] Varadhan R, Yao W, Matteini A, Beamer BA, Xue Q-L, Yang H, et al. (2014). Simple biologically informed inflammatory index of two serum cytokines predicts 10 year all-cause mortality in older adults. J Gerontol A Biol Sci Med Sci, 69:165–173.

[70] Schaum N, Lehallier B, Hahn O, Pálovics R, Hosseinzadeh S, Lee SE, et al. (2020). Ageing hallmarks exhibit organ-specific temporal signatures. Nature, 583:596–602.

[71] Mogilenko DA, Shchukina I, Artyomov MN (2022). Immune ageing at single-cell resolution. Nat Rev Immunol, 22:484–498.

[72] Mogilenko DA, Shpynov O, Andhey PS, Arthur L, Swain A, Esaulova E, et al. (2021). Comprehensive Profiling of an Aging Immune System Reveals Clonal GZMK+ CD8+ T Cells as Conserved Hallmark of Inflammaging. Immunity, 54:99-115.e12.

[73] Li M, Yao D, Zeng X, Kasakovski D, Zhang Y, Chen S, et al. (2019). Age related human T cell subset evolution and senescence. Immun Ageing A, 16:24.

[74] Aw D, Silva AB, Palmer DB (2007). Immunosenescence: emerging challenges for an ageing population. Immunology, 120:435–446.

[75] Beerman I, Maloney WJ, Weissmann IL, Rossi DJ (2010). Stem cells and the aging hematopoietic system. Curr Opin Immunol, 22:500–506.

[76] Goronzy JJ, Weyand CM (2019). Mechanisms underlying T cell ageing. Nat Rev Immunol, 19:573–583.

[77] Nikolich-Žugich J (2018). The twilight of immunity: emerging concepts in aging of the immune system. Nat Immunol, 19:10–19.

[78] Lal H, Cunningham AL, Godeaux O, Chlibek R, Diez-Domingo J, Hwang S-J, et al. (2015). Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. N Engl J Med, 372:2087–2096.

[79] Walsh EE, Frenck RW, Falsey AR, Kitchin N, Absalon J, Gurtman A, et al. (2020). Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. N Engl J Med, 383:2439–2450.

[80] Sturmlechner I, Jain A, Hu B, Jadhav RR, Cao W, Okuyama H, et al. (2025). Antigen specificity shapes distinct aging trajectories of memory $CD8^+$ T cells. Nat Commun, 16:6394.

[81] Zeidan RS, McElroy T, Rathor L, Martenson MS, Lin Y, Mankowski RT (2023). Sex differences in frailty among older adults. Exp Gerontol, 184:112333.

[82] Klein SL, Flanagan KL (2016). Sex differences in immune responses. Nat Rev Immunol, 16:626–638.

[83] Giefing-Kröll C, Berger P, Lepperdinger G, Grubeck-Loebenstein B (2015). How sex and age affect immune responses, susceptibility to infections, and response to vaccination. Aging Cell, 14:309–321.

[84] Hannah MF, Bajic VB, Klein SL (2008). Sex differences in the recognition of and innate antiviral responses to Seoul virus in Norway rats. Brain Behav Immun, 22:503–516.

[85] Klein SL, Flanagan KL (2016). Sex differences in immune responses. Nat Rev Immunol, 16:626–638.

[86] Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G (2019). Sex differences in vaccine-induced humoral immunity. Semin Immunopathol, 41:239–249.

[87] Markle JG, Fish EN (2014). SeXX matters in immunity. Trends Immunol, 35:97–104.

[88] Kovats S (2015). Estrogen receptors regulate innate immune cells and signaling pathways. Cell Immunol, 294:63–69.

[89] Klinge CM (2008). Estrogenic control of mitochondrial function and biogenesis. J Cell Biochem, 105:1342–1351.

[90] Kalaitzidis D, Gilmore TD (2005). Transcription factor cross-talk: the estrogen receptor and NF-kappaB. Trends Endocrinol Metab TEM, 16:46–52.

[91] Vegeto E, Bonincontro C, Pollio G, Sala A, Viappiani S, Nardi F, et al. (2001). Estrogen prevents the lipopolysaccharide-induced inflammatory response in microglia. J Neurosci Off J Soc Neurosci, 21:1809–1818.

[92] Dunn SE, Ousman SS, Sobel RA, Zuniga L, Baranzini SE, Youssef S, et al. (2007). Peroxisome proliferator-activated receptor (PPAR)alpha expression in T cells mediates gender differences in development of T cell-mediated autoimmunity. J Exp Med, 204:321–330.

[93] Bianchi VE (2019). The Anti-Inflammatory Effects of Testosterone. J Endocr Soc, 3:91–107.

[94] Pace S, Werz O (2020). Impact of Androgens on Inflammation-Related Lipid Mediator Biosynthesis in Innate Immune Cells. Front Immunol, 11:1356.

[95] Kim OY, Chae JS, Paik JK, Seo HS, Jang Y, Cavaillon J-M, et al. (2012). Effects of aging and menopause on serum interleukin-6 levels and peripheral blood mononuclear cell cytokine production in healthy nonobese women. Age, 34:415–425.

[96] McCarthy M, Raval AP (2020). The peri-menopause in a woman's life: a systemic inflammatory phase that enables later neurodegenerative disease. J Neuroinflammation, 17:317.

[97] Kim OY, Chae JS, Paik JK, Seo HS, Jang Y, Cavaillon J-M, et al. (2012). Effects of aging and menopause on serum interleukin-6 levels and peripheral blood

mononuclear cell cytokine production in healthy nonobese women. Age, 34:415–425.

[98] Toth MJ, Tchernof A, Sites CK, Poehlman ET (2000). Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Disord J Int Assoc Study Obes, 24:226–231.

[99] Zhao W, Hou Y, Song X, Wang L, Zhang F, Zhang H, et al. (2021). Estrogen Deficiency Induces Mitochondrial Damage Prior to Emergence of Cognitive Deficits in a Postmenopausal Mouse Model. Front Aging Neurosci, 13:713819.

[100] Sites CK, Toth MJ, Cushman M, L'Hommedieu GD, Tchernof A, Tracy RP, et al. (2002). Menopause-related differences in inflammation markers and their relationship to body fat distribution and insulin-stimulated glucose disposal. Fertil Steril, 77:128–135.

[101] Ong S-M, Hadadi E, Dang T-M, Yeap W-H, Tan CT-Y, Ng T-P, et al. (2018). The pro-inflammatory phenotype of the human non-classical monocyte subset is attributed to senescence. Cell Death Dis, 9:266.

[102] Gameiro CM, Romão F, Castelo-Branco C (2010). Menopause and aging: changes in the immune system--a review. Maturitas, 67:316–320.

[103] De Maeyer RPH, Sikora J, Bracken OV, Shih B, Lloyd AF, Peckham H, et al. (2025). Age-Associated Inflammatory Monocytes Are Increased in Menopausal Females and Reversed by Hormone Replacement Therapy. Aging Cell, 24:e70249.

[104] Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR, Baltimore Longitudinal Study of Aging (2001). Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab, 86:724–731.

[105] Zou H, Zhao J, Xu H, Chen W, Cao R, Ma Y (2025). Androgens Are a Key Factor Affecting Immune Related Diseases. World J Mens Health. doi: 10.5534/wjmh.240292.

[106] Klein SL, Flanagan KL (2016). Sex differences in immune responses. Nat Rev Immunol, 16:626–638.

[107] Navarro G, Allard C, Xu W, Mauvais-Jarvis F (2015). The role of androgens in metabolism, obesity, and diabetes in males and females. Obesity, 23:713–719.

[108] Casas R, Sacanella E, Urpí-Sardà M, Chiva-Blanch G, Ros E, Martínez-González M-A, et al. (2014). The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. PloS One, 9:e100084.

[109] Wu P-Y, Chen K-M, Tsai W-C (2020). The Mediterranean Dietary Pattern and Inflammation in Older Adults: A Systematic Review and Meta-analysis. Adv Nutr, 12:363–373.

[110] Flynn MG, McFarlin BK, Markofski MM (2007). The Anti-Inflammatory Actions of Exercise Training. Am J Lifestyle Med, 1:220–235.

[111] Irwin MR (2015). Why sleep is important for health: a psychoneuroimmunology perspective. Annu Rev Psychol, 66:143–172.

[112] Cornman JC, Glei DA, Goldman N, Ryff CD, Weinstein M (2015). Socioeconomic Status and Biological Markers of Health: An Examination of Adults in the United States and Taiwan. J Aging Health, 27:75–102.

[113] Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. (2012). Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc Natl Acad Sci U S A, 109:5995–5999.

[114] Surachman A, Jenkins AIC, Santos AR, Almeida DM (2021). Socioeconomic Status Trajectories across the Life Course, Daily Discrimination, and Inflammation among Black and White Adults. Psychoneuroendocrinology, 127:105193.

[115] Friedman EM, Herd P (2010). Income, Education, and Inflammation: Differential Associations in a National Probability Sample (The MIDUS Study). Psychosom Med, 72:290–300.

[116] Müller L, Di Benedetto S (2024). Immunosenescence and Cytomegalovirus: Exploring Their Connection in the Context of Aging, Health, and Disease. Int J Mol Sci, 25:753.

[117] Yoo JY, Groer M, Dutra SVO, Sarkar A, McSkimming DI (2020). Gut Microbiota and Immune System Interactions. Microorganisms, 8:1587.

[118] Serafini MM, Maddalon A, Iulini M, Galbiati V (2022). Air Pollution: Possible Interaction between the Immune and Nervous System? Int J Environ Res Public Health, 19:16037.

[119] Costa DV de P, Lopes MS, Mendonça R de D, Malta DC, Freitas PP de, Lopes ACS (2021). Food consumption differences in Brazilian urban and rural areas: the National Health Survey. Cienc Saude Coletiva, 26:3805–3813.

[120] Kalyakulina A, Yusipov I, Kondakova E, Sivtseva T, Zakharova R, Semenov S, et al. (2024). Inflammaging Markers in the Extremely Cold Climate: A Case Study of Yakutian Population. Int J Mol Sci, 25:13741.

[121] Smith AJP, Humphries SE (2009). Cytokine and cytokine receptor gene polymorphisms and their functionality. Cytokine Growth Factor Rev, 20:43–59.

[122] Dai L, Liu D, Guo H, Wang Y, Bai Y (2012). Association between polymorphism in the promoter region of Interleukin 6 (-174 G/C) and risk of Alzheimer's disease: a meta-analysis. J Neurol, 259:414–419.

[123] Hou H, Wang C, Sun F, Zhao L, Dun A, Sun Z (2015). Association of interleukin-6 gene polymorphism with coronary artery disease: an updated systematic review and cumulative meta-analysis. Inflamm Res Off J Eur Histamine Res Soc Al, 64:707–720.

[124] Teissier T, Boulanger E, Cox LS (2022). Interconnections between Inflammageing and Immunosenescence during Ageing. Cells, 11:359.

[125] Fulop T, Larbi A, Dupuis G, Le Page A, Frost EH, Cohen AA, et al. (2017). Immunosenescence and Inflamm-Aging As Two Sides of the Same Coin: Friends or Foes? Front Immunol, 8:1960.

[126] Abdallah YEH, Chahal S, Jamali F, Mahmoud SH (2023). Drug-disease interaction: Clinical consequences of inflammation on drugs action and disposition. J Pharm

Pharm Sci Publ Can Soc Pharm Sci Soc Can Sci Pharm, 26:11137.
[127] Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. (2013). Frailty consensus: a call to action. J Am Med Dir Assoc, 14:392–397.
[128] Pansarasa O, Pistono C, Davin A, Bordoni M, Mimmi MC, Guaita A, et al. (2019). Altered immune system in frailty: Genetics and diet may influence inflammation. Ageing Res Rev, 54:100935.
[129] Cesari M, Pérez-Zepeda MU, Marzetti E (2017). Frailty and Multimorbidity: Different Ways of Thinking About Geriatrics. J Am Med Dir Assoc, 18:361–364.
[130] Pothier K, Gana W, Bailly N, Fougère B (2022). Associations Between Frailty and Inflammation, Physical, and Psycho-Social Health in Older Adults: A Systematic Review. Front Psychol, 13:805501.
[131] Bleve A, Motta F, Durante B, Pandolfo C, Selmi C, Sica A (2023). Immunosenescence, Inflammaging, and Frailty: Role of Myeloid Cells in Age-Related Diseases. Clin Rev Allergy Immunol, 64:123–144.
[132] Wilson D, Jackson T, Sapey E, Lord JM (2017). Frailty and sarcopenia: The potential role of an aged immune system. Ageing Res Rev, 36:1–10.
[133] Qu T, Yang H, Walston JD, Fedarko NS, Leng SX (2009). Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. Cytokine, 46:319–324.
[134] Arosio B, Ferri E, Mari D, Tobaldini E, Vitale G, Montano N (2023). The influence of inflammation and frailty in the aging continuum. Mech Ageing Dev, 215:111872.
[135] Bålsrud P, Ulven SM, Christensen JJ, Ottestad I, Holven KB (2024). Inflammatory markers and frailty in home-dwelling elderly, a cross-sectional study. BMC Geriatr, 24:175.
[136] Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K (2008). A standard procedure for creating a frailty index. BMC Geriatr, 8:24.
[137] Byrne T, Cooke J, Bambrick P, McNeela E, Harrison M (2023). Circulating inflammatory biomarker responses in intervention trials in frail and sarcopenic older adults: A systematic review and meta-analysis. Exp Gerontol, 177:112199.
[138] Caldo-Silva A, Furtado GE, Chupel MU, Bachi ALL, de Barros MP, Neves R, et al. (2021). Effect of Training-Detraining Phases of Multicomponent Exercises and BCAA Supplementation on Inflammatory Markers and Albumin Levels in Frail Older Persons. Nutrients, 13:1106.
[139] Belloni G, Cesari M (2019). Frailty and Intrinsic Capacity: Two Distinct but Related Constructs. Front Med, 6:133.
[140] Beavers DP, Kritchevsky SB, Gill TM, Ambrosius WT, Anton SD, Fielding RA, et al. (2021). Elevated IL-6 and CRP Levels Are Associated With Incident Self-Reported Major Mobility Disability: A Pooled Analysis of Older Adults With Slow Gait Speed. J Gerontol A Biol Sci Med Sci, 76:2293–2299.
[141] Cox MC, Booth M, Ghita G, Wang Z, Gardner A, Hawkins RB, et al. (2021). The impact of sarcopenia and acute muscle mass loss on long-term outcomes in critically ill patients with intra-abdominal sepsis. J Cachexia Sarcopenia Muscle, 12:1203–1213.
[142] Liang Z, Zhang T, Liu H, Li Z, Peng L, Wang C, et al. (2022). Inflammaging: The ground for sarcopenia? Exp Gerontol, 168:111931.
[143] Beyer I, Mets T, Bautmans I (2012). Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care, 15:12–22.
[144] Taniguchi K, Karin M (2018). NF-κB, inflammation, immunity and cancer: coming of age. Nat Rev Immunol, 18:309–324.
[145] Karanth SD, Washington C, Cheng T-YD, Zhou D, Leeuwenburgh C, Braithwaite D, et al. (2021). Inflammation in Relation to Sarcopenia and Sarcopenic Obesity among Older Adults Living with Chronic Comorbidities: Results from the National Health and Nutrition Examination Survey 1999-2006. Nutrients, 13:3957.
[146] Boccardi V, Orr ME, Polidori MC, Ruggiero C, Mecocci P (2024). Focus on senescence: Clinical significance and practical applications. J Intern Med, 295:599–619.
[147] Geiger H, de Haan G, Florian MC (2013). The ageing haematopoietic stem cell compartment. Nat Rev Immunol, 13:376–389.
[148] Shafqat A, Khan S, Omer MH, Niaz M, Albalkhi I, AlKattan K, et al. (2023). Cellular senescence in brain aging and cognitive decline. Front Aging Neurosci, 15:1281581.
[149] Wissler Gerdes EO, Zhu Y, Weigand BM, Tripathi U, Burns TC, Tchkonia T, et al. (2020). Cellular senescence in aging and age-related diseases: Implications for neurodegenerative diseases. Int Rev Neurobiol, 155:203–234.
[150] Thériault P, ElAli A, Rivest S (2015). The dynamics of monocytes and microglia in Alzheimer's disease. Alzheimers Res Ther, 7:41.
[151] Surmeier DJ, Guzman JN, Sanchez-Padilla J (2010). Calcium, cellular aging, and selective neuronal vulnerability in Parkinson's disease. Cell Calcium, 47:175–182.
[152] Pajares M, I Rojo A, Manda G, Boscá L, Cuadrado A (2020). Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. Cells, 9:1687.
[153] Tjalkens RB, Popichak KA, Kirkley KA (2017). Inflammatory Activation of Microglia and Astrocytes in Manganese Neurotoxicity. Adv Neurobiol, 18:159–181.
[154] Feng L, Wang Y, Zeng D, Wang M, Duan X (2023). Predictors of cognitive decline in older individuals without dementia: An updated meta-analysis. Ann Clin Transl Neurol, 10:497–506.
[155] Behfar Q, Ramirez Zuniga A, Martino-Adami PV (2022). Aging, Senescence, and Dementia. J Prev Alzheimers Dis, 9:523–531.
[156] Di Lazzaro G, Picca A, Boldrini S, Bove F, Marzetti E, Petracca M, et al. (2024). Differential profiles of serum

cytokines in Parkinson's disease according to disease duration. Neurobiol Dis, 190:106371.
[157] Garcia J (2025). Early Safety/Therapeutic Impact Results of ALT-100 eNAMPT mAb in the PUERTA Phase 2A ARDS Trial. Am J Resp Crit Care Med .
[158] Sun BL, Sun X, Casanova N, Garcia AN, Oita R, Algotar AM, et al. (2020). Role of secreted extracellular nicotinamide phosphoribosyltransferase (eNAMPT) in prostate cancer progression: Novel biomarker and therapeutic target. EBioMedicine, 61:103059.
[159] Moore KJ, Sheedy FJ, Fisher EA (2013). Macrophages in atherosclerosis: a dynamic balance. Nat Rev Immunol, 13:709–721.
[160] Barbé-Tuana F, Funchal G, Schmitz CRR, Maurmann RM, Bauer ME (2020). The interplay between immunosenescence and age-related diseases. Semin Immunopathol, 42:545–557.
[161] IL6R Genetics Consortium Emerging Risk Factors Collaboration, Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, et al. (2012). Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet, 379:1205–1213.
[162] Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium, Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JEL, Shah T, et al. (2012). The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis. Lancet, 379:1214–1224.
[163] Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. (2017). Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med, 377:1119–1131.
[164] Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, et al. (2020). Colchicine in Patients with Chronic Coronary Disease. N Engl J Med, 383:1838–1847.
[165] Alpert A, Pickman Y, Leipold M, Rosenberg-Hasson Y, Ji X, Gaujoux R, et al. (2019). A clinically meaningful metric of immune age derived from high-dimensional longitudinal monitoring. Nat Med, 25:487–495.
[166] Ahadi S, Zhou W, Schüssler-Fiorenza Rose SM, Sailani MR, Contrepois K, Avina M, et al. (2020). Personal aging markers and ageotypes revealed by deep longitudinal profiling. Nat Med, 26:83–90.
[167] Tanaka T, Basisty N, Fantoni G, Candia J, Moore AZ, Biancotto A, et al. (2020). Plasma proteomic biomarker signature of age predicts health and life span. eLife, 9:e61073.
[168] He J, Li J, Li Y, Xu Z, Ma M, Chen H, et al. (2024). Single-cell transcriptomics identifies senescence-associated secretory phenotype (SASP) features of testicular aging in human. Aging, 16:3350–3362.
[169] Schafer MJ, Zhang X, Kumar A, Atkinson EJ, Zhu Y, Jachim S, et al. (2020). The senescence-associated secretome as an indicator of age and medical risk. JCI Insight, 5:e133668, 133668.
[170] Freiesleben T, Grote T (2023). Beyond generalization: a theory of robustness in machine learning. Synthese, 202:109.
[171] Chekroud AM, Hawrilenko M, Loho H, Bondar J, Gueorguieva R, Hasan A, et al. (2024). Illusory generalizability of clinical prediction models. Science, 383:164–167.
[172] Gygi JP, Kleinstein SH, Guan L (2023). Predictive overfitting in immunological applications: Pitfalls and solutions. Hum Vaccines Immunother, 19:2251830.
[173] Improving generalization of machine learning-identified biomarkers using causal modelling with examples from immune receptor diagnostics | Nature Machine Intelligence. https://www.nature.com/articles/s42256-023-00781-8. Accessed 16 Mar 2026.
[174] Mo X, Chen X, Ieong C, Zhang S, Li H, Li J, et al. (2020). Early Prediction of Clinical Response to Etanercept Treatment in Juvenile Idiopathic Arthritis Using Machine Learning. Front Pharmacol, 11:1164.
[175] MacEachern SJ, Forkert ND (2021). Machine learning for precision medicine. Genome, 64:416–425.
[176] Tumurkhuu G, Casanova NG, Kempf CL, Ercan Laguna D, Camp SM, Dagvadorj J, et al. (2023). eNAMPT/TLR4 inflammatory cascade activation is a key contributor to SLE Lung vasculitis and alveolar hemorrhage. J Transl Autoimmun, 6:100181.
[177] Bhardwaj T, Sumangali K (2025). An explainable federated blockchain framework with privacy-preserving AI optimization for securing healthcare data. Sci Rep, 15:21799.
[178] Cheng Z, Wu Y, Li Y, Cai L, Ihnaini B (2025). A Comprehensive Review of Explainable Artificial Intelligence (XAI) in Computer Vision. Sensors, 25:4166.
[179] Kuehnemann C, Hu K-Q, Butera K, Patel SK, Bons J, Schilling B, et al. (2022). Extracellular Nicotinamide Phosphoribosyltransferase Is a Component of the Senescence-Associated Secretory Phenotype. Front Endocrinol, 13:935106.
[180] Casanova NG, Herazo-Maya JD, Kempf CL, Sun BL, Song JH, Hernandez A, et al. (2025). eNAMPT Is a Novel DAMP and Therapeutic Target in Human and Murine Pulmonary Fibrosis. Am J Respir Cell Mol Biol, 73:572–585.
[181] Casanova NG, Herazo-Maya JD, Kempf CL, Sun BL, Song JH, Hernandez A, et al. (2025). eNAMPT Is a Novel DAMP and Therapeutic Target in Human and Murine Pulmonary Fibrosis. Am J Respir Cell Mol Biol, 73:572–585.
[182] Khosla S, Farr JN, Tchkonia T, Kirkland JL (2020). The role of cellular senescence in ageing and endocrine disease. Nat Rev Endocrinol, 16:263–275.
[183] Hickson LJ, Langhi Prata LGP, Bobart SA, Evans TK, Giorgadze N, Hashmi SK, et al. (2019). Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease. EBioMedicine, 47:446–456.
[184] Kirkland JL, Tchkonia T (2020). Senolytic drugs: from discovery to translation. J Intern Med, 288:518–536.
[185] Zhu Y, Tchkonia T, Pirtskhalava T, Gower AC, Ding H, Giorgadze N, et al. (2015). The Achilles' heel of

senescent cells: from transcriptome to senolytic drugs. Aging Cell, 14:644–658.

[186] Demaria M, Ohtani N, Youssef SA, Rodier F, Toussaint W, Mitchell JR, et al. (2014). An essential role for senescent cells in optimal wound healing through secretion of PDGF-AA. Dev Cell, 31:722–733.

[187] Zhang L, Pitcher LE, Prahalad V, Niedernhofer LJ, Robbins PD (2023). Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. FEBS J, 290:1362–1383.

[188] Lagoumtzi SM, Chondrogianni N (2021). Senolytics and senomorphics: Natural and synthetic therapeutics in the treatment of aging and chronic diseases. Free Radic Biol Med, 171:169–190.

[189] Fu TE, Zhou Z (2025). Senescent cells as a target for anti-aging interventions: From senolytics to immune therapies. J Transl Intern Med, 13:33–47.

[190] Fu TE, Zhou Z Senescent cells as a target for anti-aging interventions: From senolytics to immune therapies. J Transl Intern Med, 13:33–47.

[191] Yang D, Sun B, Li S, Wei W, Liu X, Cui X, et al. (2023). NKG2D-CAR T cells eliminate senescent cells in aged mice and nonhuman primates. Sci Transl Med, 15:eadd1951.

[192] Amor C, Feucht J, Leibold J, Ho Y-J, Zhu C, Alonso-Curbelo D, et al. (2020). Senolytic CAR T cells reverse senescence-associated pathologies. Nature, 583:127–132.

[193] Wang S, Huo T, Lu M, Zhao Y, Zhang J, He W, et al. (2025). Recent Advances in Aging and Immunosenescence: Mechanisms and Therapeutic Strategies. Cells, 14:499.

[194] Martel J, Ojcius DM, Young JD (2024). Lifestyle interventions to delay senescence. Biomed J, 47:100676.

[195] Landberg R, Sun Q, Rimm EB, Cassidy A, Scalbert A, Mantzoros CS, et al. (2011). Selected dietary flavonoids are associated with markers of inflammation and endothelial dysfunction in U.S. women. J Nutr, 141:618–625.

[196] Sigal RJ, Kenny GP, Boulé NG, Wells GA, Prud'homme D, Fortier M, et al. (2007). Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med, 147:357–369.

[197] Kirwan JP, Barkoukis H, Brooks LM, Marchetti CM, Stetzer BP, Gonzalez F (2009). Exercise training and dietary glycemic load may have synergistic effects on insulin resistance in older obese adults. Ann Nutr Metab, 55:326–333.

[198] Park MH, Kim DH, Lee EK, Kim ND, Im DS, Lee J, et al. (2014). Age-related inflammation and insulin resistance: a review of their intricate interdependency. Arch Pharm Res, 37:1507–1514.

[199] Mora I, Arola L, Caimari A, Escoté X, Puiggròs F (2022). Structured Long-Chain Omega-3 Fatty Acids for Improvement of Cognitive Function during Aging. Int J Mol Sci, 23:3472.

[200] Tyrovolas S, Haro JM, Foscolou A, Tyrovola D, Mariolis A, Bountziouka V, et al. (2018). Anti-Inflammatory Nutrition and Successful Ageing in Elderly Individuals: The Multinational MEDIS Study. Gerontology, 64:3–10.

[201] Manoogian ENC, Wilkinson MJ, O'Neal M, Laing K, Nguyen J, Van D, et al. (2024). Time-Restricted Eating in Adults With Metabolic Syndrome : A Randomized Controlled Trial. Ann Intern Med, 177:1462–1470.

[202] Mendham AE, Goedecke JH, Zeng Y, Larsen S, George C, Hauksson J, et al. (2021). Exercise training improves mitochondrial respiration and is associated with an altered intramuscular phospholipid signature in women with obesity. Diabetologia, 64:1642–1659.

[203] Lemos G de O, Torrinhas RS, Waitzberg DL (2023). Nutrients, Physical Activity, and Mitochondrial Dysfunction in the Setting of Metabolic Syndrome. Nutrients, 15:1217.

[204] Du PY, Gandhi A, Bawa M, Gromala J (2023). The ageing immune system as a potential target of senolytics. Oxf Open Immunol, 4:iqad004.

[205] Fu Y, Wang B, Alu A, Hong W, Lei H, He X, et al. (2025). Immunosenescence: signaling pathways, diseases and therapeutic targets. Signal Transduct Target Ther, 10:250.

[206] Delrue C, Speeckaert R, Speeckaert MM (2025). Rewinding the Clock: Emerging Pharmacological Strategies for Human Anti-Aging Therapy. Int J Mol Sci, 26:9372.

[207] Li X, Li C, Zhang W, Wang Y, Qian P, Huang H (2023). Inflammation and aging: signaling pathways and intervention therapies. Signal Transduct Target Ther, 8:239.

[208] Fülöp T, Larbi A, Witkowski JM (2019). Human Inflammaging. Gerontology, 65:495–504.

[209] Seng NT (1987). Temporary cardiac pacing at the bedside. Med J Malaysia, 42:86–89.

[210] Bektas A, Schurman SH, Sen R, Ferrucci L (2018). Aging, inflammation and the environment. Exp Gerontol, 105:10–18.

[211] Flynn MG, Markofski MM, Carrillo AE (2019). Elevated Inflammatory Status and Increased Risk of Chronic Disease in Chronological Aging: Inflamm-aging or Inflamm-inactivity? Aging Dis, 10:147–156.

[212] Holman HR (2020). The Relation of the Chronic Disease Epidemic to the Health Care Crisis. ACR Open Rheumatol, 2:167–173.

[213] Hajat C, Stein E (2018). The global burden of multiple chronic conditions: A narrative review. Prev Med Rep, 12:284–293.

[214] Chapel JM, Ritchey MD, Zhang D, Wang G (2017). Prevalence and Medical Costs of Chronic Diseases Among Adult Medicaid Beneficiaries. Am J Prev Med, 53:S143–S154.

[215] Dupont J, Antonio L, Dedeyne L, O'Neill TW, Vanderschueren D, Rastrelli G, et al. (2021). Inflammatory markers are associated with quality of life, physical activity, and gait speed but not sarcopenia in aged men (40-79 years). J Cachexia Sarcopenia Muscle, 12:1818–1831.

[216] Alberro A, Iribarren-Lopez A, Sáenz-Cuesta M, Matheu A, Vergara I, Otaegui D (2021). Inflammaging markers

characteristic of advanced age show similar levels with frailty and dependency. Sci Rep, 11:4358.
[217] Strianese O, Rizzo F, Ciccarelli M, Galasso G, D'Agostino Y, Salvati A, et al. (2020). Precision and Personalized Medicine: How Genomic Approach Improves the Management of Cardiovascular and Neurodegenerative Disease. Genes, 11:747.
[218] Leonardi GC, Accardi G, Monastero R, Nicoletti F, Libra M (2018). Ageing: from inflammation to cancer. Immun Ageing A, 15:1.
[219] Fane M, Weeraratna AT (2020). How the ageing microenvironment influences tumour progression. Nat Rev Cancer, 20:89–106.
[220] Sun BL, Tang L, Sun X, Garcia AN, Camp SM, Posadas E, et al. (2021). A Humanized Monoclonal Antibody Targeting Extracellular Nicotinamide Phosphoribosyltransferase Prevents Aggressive Prostate Cancer Progression. Pharmaceuticals, 14:1322.
[221] Knüpfer H, Preiss R (2007). Significance of interleukin-6 (IL-6) in breast cancer (review). Breast Cancer Res Treat, 102:129–135.
[222] Saintigny P, Massarelli E, Lin S, Ahn Y-H, Chen Y, Goswami S, et al. (2013). CXCR2 expression in tumor cells is a poor prognostic factor and promotes invasion and metastasis in lung adenocarcinoma. Cancer Res, 73:571–582.
[223] Velarde MC, Demaria M, Campisi J (2013). Senescent cells and their secretory phenotype as targets for cancer therapy. Interdiscip Top Gerontol, 38:17–27.
[224] Wang T, Notta F, Navab R, Joseph J, Ibrahimov E, Xu J, et al. (2017). Senescent Carcinoma-Associated Fibroblasts Upregulate IL8 to Enhance Prometastatic Phenotypes. Mol Cancer Res MCR, 15:3–14.
[225] Kim YH, Choi YW, Lee J, Soh EY, Kim J-H, Park TJ (2017). Senescent tumor cells lead the collective invasion in thyroid cancer. Nat Commun, 8:15208.
[226] Gao J, Zhao S, Halstensen TS (2016). Increased interleukin-6 expression is associated with poor prognosis and acquired cisplatin resistance in head and neck squamous cell carcinoma. Oncol Rep, 35:3265–3274.
[227] Merline R, Moreth K, Beckmann J, Nastase MV, Zeng-Brouwers J, Tralhão JG, et al. (2011). Signaling by the matrix proteoglycan decorin controls inflammation and cancer through PDCD4 and MicroRNA-21. Sci Signal, 4:ra75.
[228] Fabbri M, Paone A, Calore F, Galli R, Gaudio E, Santhanam R, et al. (2012). MicroRNAs bind to Toll-like receptors to induce prometastatic inflammatory response. Proc Natl Acad Sci U S A, 109:E2110-2116.
[229] Travelli C, Colombo G, Aliotta M, Fagiani F, Fava N, De Sanctis R, et al. (2023). Extracellular nicotinamide phosphoribosyltransferase (eNAMPT) neutralization counteracts T cell immune evasion in breast cancer. J Immunother Cancer, 11:e007010.
[230] Carpenter VJ, Saleh T, Gewirtz DA (2021). Senolytics for Cancer Therapy: Is All That Glitters Really Gold? Cancers, 13:723.
[231] Bleve A, Motta F, Durante B, Pandolfo C, Selmi C, Sica A (2023). Immunosenescence, Inflammaging, and Frailty: Role of Myeloid Cells in Age-Related Diseases. Clin Rev Allergy Immunol, 64:123–144.
[232] Ferrucci L, Fabbri E (2018). Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol, 15:505–522.
[233] Kim H-J, Higashimori T, Park S-Y, Choi H, Dong J, Kim Y-J, et al. (2004). Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. Diabetes, 53:1060–1067.
[234] Zaragosi L-E, Wdziekonski B, Villageois P, Keophiphath M, Maumus M, Tchkonia T, et al. (2010). Activin a plays a critical role in proliferation and differentiation of human adipose progenitors. Diabetes, 59:2513–2521.
[235] Palmer AK, Xu M, Zhu Y, Pirtskhalava T, Weivoda MM, Hachfeld CM, et al. (2019). Targeting senescent cells alleviates obesity-induced metabolic dysfunction. Aging Cell, 18:e12950.
[236] Odegaard AO, Jacobs DR, Sanchez OA, Goff DC, Reiner AP, Gross MD (2016). Oxidative stress, inflammation, endothelial dysfunction and incidence of type 2 diabetes. Cardiovasc Diabetol, 15:51.
[237] Aryan Z, Ghajar A, Faghihi-Kashani S, Afarideh M, Nakhjavani M, Esteghamati A (2018). Baseline High-Sensitivity C-Reactive Protein Predicts Macrovascular and Microvascular Complications of Type 2 Diabetes: A Population-Based Study. Ann Nutr Metab, 72:287–295.
[238] Ogrodnik M, Miwa S, Tchkonia T, Tiniakos D, Wilson CL, Lahat A, et al. (2017). Cellular senescence drives age-dependent hepatic steatosis. Nat Commun, 8:15691.
[239] Maeso-Díaz R, Gracia-Sancho J (2020). Aging and Chronic Liver Disease. Semin Liver Dis, 40:373–384.
[240] Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, et al. (2008). Senescence of activated stellate cells limits liver fibrosis. Cell, 134:657–667.
[241] Krizhanovsky V, Yon M, Dickins RA, Hearn S, Simon J, Miething C, et al. (2008). Senescence of activated stellate cells limits liver fibrosis. Cell, 134:657–667.
[242] Wijayasiri P, Astbury S, Kaye P, Oakley F, Alexander GJ, Kendall TJ, et al. (2022). Role of Hepatocyte Senescence in the Activation of Hepatic Stellate Cells and Liver Fibrosis Progression. Cells, 11:2221.
[243] Loo TM, Kamachi F, Watanabe Y, Yoshimoto S, Kanda H, Arai Y, et al. (2017). Gut Microbiota Promotes Obesity-Associated Liver Cancer through PGE2-Mediated Suppression of Antitumor Immunity. Cancer Discov, 7:522–538.
[244] Fabregat I, Moreno-Càceres J, Sánchez A, Dooley S, Dewidar B, Giannelli G, et al. (2016). TGF-β signalling and liver disease. FEBS J, 283:2219–2232.
[245] Sun BL, Sun X, Kempf CL, Song JH, Casanova NG, Camp SM, et al. (2023). Involvement of eNAMPT/TLR4 inflammatory signaling in progression of non-alcoholic fatty liver disease, steatohepatitis, and fibrosis. FASEB J Off Publ Fed Am Soc Exp Biol, 37:e22825.