

REVIEW ARTICLE

Inflammaging as a systems-level integrator of disease: Biological foundations of chronic low-grade inflammation

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Abstract

The concept of inflammaging—defined as the persistent, low-grade inflammatory state accompanying biological aging—has emerged as a unifying framework for understanding chronic disease in later life. Unlike acute inflammation, which is adaptive, transient, and protective, inflammaging reflects persistent dysregulation of immune signaling, impaired resolution of inflammatory responses, mitochondrial decline, and progressive loss of tissue homeostasis. Evidence increasingly indicates that inflammaging is not merely a consequence of aging but an active systems-level process that reshapes metabolic, vascular, neurological, and musculoskeletal physiology. Sustained inflammatory activation contributes to frailty, cardiovascular disease, neurodegeneration, sarcopenia, metabolic dysfunction, and osteoarthritis through interconnected molecular and cellular mechanisms involving immunosenescence, cellular senescence, oxidative stress, inflammasome activation, and epigenetic remodeling. Recent advances in geroscience have reframed inflammation as a multidirectional biological network integrating immune, endocrine, metabolic, microbiological, and biomechanical signals. This perspective moves beyond reductionist cytokine models by conceptualizing inflammation as a distributed regulatory architecture operating across tissues and organ systems. Accordingly, chronic disease may arise not only from local organ pathology but also from progressive failure of intersystem communication and adaptive resilience. This review examines the biological foundations of inflammaging, emphasizing immunosenescence, senescence-associated secretory pathways, mitochondrial dysfunction, inflammasome biology, cytokine network dynamics, and epigenetic regulation. We propose that inflammaging is best understood as multiscale biological interface failure, in which persistent inflammatory signaling progressively destabilizes tissue integration across physiological systems. This framework may support the development of more precise biomarkers, systems-oriented therapeutic strategies, and translational interventions designed to extend health span rather than merely prolong survival.

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1. Introduction

Inflammaging is recognized as a chronic, low-grade inflammatory state associated with biological aging, frailty, sarcopenia, cardiovascular disease, metabolic dysfunction, neurodegeneration, and osteoarthritis. Established mechanisms include immunosenescence, cellular senescence, senescence-associated secretory phenotype (SASP) activation, mitochondrial dysfunction, oxidative stress, inflammasome signaling, and cytokine network dysregulation.

This review conceptualizes inflammaging as a multiscale interface failure rather than a simple cytokine-driven process. It integrates immune, metabolic, microbial, neuroendocrine, vascular, and musculoskeletal signaling into a unified systems framework, emphasizing how tissue-specific interfaces convert chronic inflammatory tone into clinically heterogeneous disease phenotypes.

The global demographic transition toward aging societies represents one of the defining biomedical challenges of the 21st century. Advances in sanitation, vaccination, antimicrobial therapy, cardiovascular medicine, and public health have dramatically increased life expectancy across much of the world. Yet increased longevity has not been uniformly accompanied by preservation of physiological resilience. Instead, modern medicine increasingly confronts prolonged periods of chronic disease accumulation characterized by multimorbidity, frailty, cognitive decline, musculoskeletal degeneration, and metabolic dysfunction.

Within this context, chronic low-grade inflammation has emerged as a unifying biological denominator linking many of the major disorders associated with aging. The concept of inflammaging, originally proposed to describe the persistent inflammatory phenotype observed in older individuals, has progressively evolved into a broader framework integrating immune dysregulation, metabolic disturbance, tissue degeneration, and systems biology. Unlike acute inflammation, which is tightly regulated and temporally constrained, inflammaging reflects a chronic, often sterile activation of inflammatory pathways that persists for years or decades.

Importantly, inflammaging does not typically manifest through overt inflammatory disease. Rather than producing overt inflammatory disease, this process sustains mildly but consequential elevations in key mediators—interleukin (IL)-6, tumor necrosis factor (TNF)- α , IL-1 β , and C-reactive protein (CRP)—without triggering the clinical features of acute inflammation.¹ These mediators exert pleiotropic effects across vascular, neural, endocrine, adipose, and musculoskeletal tissues,

progressively altering homeostatic regulation and reducing physiological reserve.²

Aging itself appears to generate multiple converging stimuli that can sustain chronic inflammatory activation. Cellular senescence, mitochondrial dysfunction, impaired autophagy, oxidative stress, microbiome dysbiosis, visceral adiposity, and accumulated tissue injury collectively contribute to a self-amplifying inflammatory milieu. Rather than functioning as isolated mechanisms, these processes interact dynamically through feedback loops that reinforce inflammatory signaling over time. In this sense, inflammaging may be viewed less as a singular pathway and more as an emergent systems-level property arising from cumulative regulatory instability.

The importance of this perspective becomes increasingly evident when examining the clinical heterogeneity of aging-related disease. Frailty, atherosclerosis, insulin resistance, osteoarthritis, depression, sarcopenia, neurodegeneration, and chronic kidney disease appear phenotypically distinct, yet many share overlapping inflammatory signatures. This convergence suggests that chronic disease may arise from common biological architectures that are expressed differently across tissues according to tissue-specific vulnerabilities, genetic predisposition, environmental exposures, and biomechanical context.³

Recent systems biology approaches have further reinforced this interpretation. Integrative clustering analyses incorporating metabolic and inflammatory biomarkers have identified distinct inflammatory-metabolic phenotypes associated with differential susceptibility to digestive, cardiovascular, and neurological disorders.⁴ Such findings support the concept that inflammatory signaling functions within distributed biological networks rather than isolated linear cascades, as illustrated in [Figure 1](#).

Moreover, inflammation itself is increasingly recognized as spatially and temporally heterogeneous. Signals generated within adipose tissue, skeletal muscle, synovium, vascular endothelium, or the intestinal microbiome may propagate systemically through circulating cytokines, extracellular vesicles, metabolic intermediates, and neuroimmune communication pathways. Consequently, chronic inflammation cannot be adequately understood through organ-centered models alone. Instead, inflammaging appears to represent a distributed integrative process linking local tissue perturbations to organism-wide physiological consequences.

This review explores the biological foundations of inflammaging through a systems-oriented lens. Particular attention is given to immunosenescence, innate immune

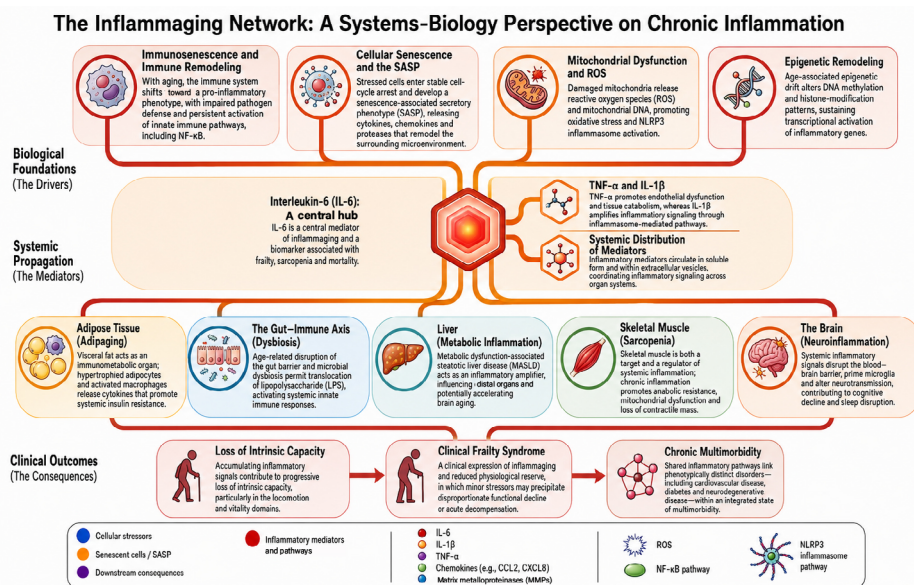


Figure 1. The inflammaging network from a systems-biology perspective on chronic inflammation, illustrating the systems-level architecture through which inflammaging propagates from molecular drivers to tissue-interface dysfunction and clinical multimorbidity. Inflammaging emerges from the interaction of multiple interconnected biological processes that collectively drive chronic low-grade inflammation during aging. Fundamental mechanisms include immunosenescence, cellular senescence with the acquisition of the SASP, mitochondrial dysfunction with reactive oxygen species generation, and age-related epigenetic remodeling. These processes converge through systemic inflammatory mediators, particularly IL-6, TNF-α, and IL-1β, which propagate inflammatory signaling across organ systems. Chronic inflammation subsequently affects multiple physiological domains, including adipose tissue, the gut-immune axis, liver metabolism, skeletal muscle, and the central nervous system, thereby promoting adiposopathy, dysbiosis, metabolic dysfunction, sarcopenia, and neuroinflammation. The cumulative consequences are progressive loss of intrinsic capacity, frailty, and multimorbidity, reflecting inflammaging as a distributed systems-level pathological network rather than an isolated immune phenomenon. Abbreviations: CCL2: C-C motif chemokine ligand 2; CXCL8: C-X-C motif chemokine ligand 8; IL: Interleukin; MMP: Matrix metalloproteinase; NF: Nuclear factor; NLRP3: NOD-like receptor family pyrin domain-containing 3; ROS: Reactive oxygen species; SASP: Senescence-associated secretory phenotype; TNF: Tumor necrosis factor.

remodeling, senescence-associated secretory pathways, mitochondrial dysfunction, inflammasome activation, and cytokine network architecture. We argue that chronic low-grade inflammation may be conceptualized as a form of multiscale interface failure in which the mechanisms ordinarily coordinating communication among tissues progressively lose regulatory precision. Such a framework may provide a more coherent understanding of chronic disease pathophysiology while simultaneously identifying novel translational opportunities.

2. Biological foundations of inflammaging

For clarity, immunosenescence, cellular senescence, and chronic inflammation are treated as linked but non-identical processes: age-related immune remodeling weakens surveillance and resolution, whereas senescent cells and their secretory phenotype can further perturb immune function and sustain inflammatory signaling.

2.1. Immunosenescence and immune remodeling

Aging is accompanied by profound alterations in both innate and adaptive immunity. Collectively termed immunosenescence, these changes extend beyond simple immune decline and instead reflect a complex process of immune remodeling characterized by impaired pathogen defense, altered inflammatory regulation, reduced antigenic diversity, and persistent activation of innate immune pathways.⁵

Progressive thymic involution curtails naïve T-cell output, narrowing the available T-cell receptor repertoire. As terminally differentiated memory T cells accumulate, immune adaptability declines further, reducing the capacity to mount effective responses against novel antigens. B-cell function similarly declines with age, impairing antibody affinity maturation and reducing the adaptability of humoral immune response.

Yet paradoxically, immunosenescence does not produce a purely immunodeficient phenotype. Instead, many older individuals exhibit chronic basal immune activation. Innate immune cells, particularly macrophages and neutrophils, frequently adopt pro-inflammatory phenotypes associated with exaggerated cytokine release and impaired inflammatory resolution.⁶

Neutrophil dysfunction includes altered chemotaxis, defective phagocytosis, dysregulated reactive oxygen species production, and abnormal neutrophil extracellular trap formation. Such changes may contribute to persistent tissue injury and endothelial dysfunction.

Macrophage remodeling appears particularly important in the biology of inflammaging. Age-associated macrophages exhibit altered metabolic programming, mitochondrial dysfunction, impaired efferocytosis, and sustained activation of nuclear factor (NF)- κ B signaling pathways. This phenotype promotes chronic secretion of IL-6, TNF- α , and other inflammatory mediators, thereby perpetuating systemic inflammatory tone. Importantly, these changes are strongly influenced by local tissue microenvironments, highlighting the contextual nature of inflammatory activation.⁷ Immunosenescence also affects regulatory mechanisms ordinarily responsible for inflammatory termination. Reduced regulatory T-cell function, impaired production of pro-resolving mediators, and altered anti-inflammatory cytokine signaling collectively diminish the capacity to restore immune equilibrium following physiological stressors. Consequently, inflammatory responses become prolonged, inefficient, and increasingly maladaptive.⁸

Emerging evidence further suggests that immune remodeling interacts bidirectionally with metabolic dysfunction. Obesity, insulin resistance, and visceral adiposity amplify inflammatory activation through adipose tissue macrophage recruitment and altered adipokine secretion, while inflammatory cytokines themselves impair insulin signaling and mitochondrial metabolism. This reciprocal interaction forms the basis of immunometabolism, a rapidly expanding field examining the integration of metabolic and immune regulation.⁹

Importantly, inflammaging is heterogeneous rather than uniform across individuals. Some older adults maintain relatively preserved immune function despite advanced chronological age, whereas others develop accelerated inflammatory phenotypes associated with frailty and multimorbidity. Such variability highlights the importance of biological aging rather than chronological aging alone.¹⁰

2.2. Cellular senescence, immune surveillance, and the senescence-associated secretory phenotype

Cellular senescence constitutes another major pillar of inflammaging biology. Initially described as an irreversible form of cell-cycle arrest, senescence is now recognized as a complex stress response triggered by telomere attrition, DNA damage, oxidative stress, oncogenic signaling, mitochondrial dysfunction, and mechanical injury.¹¹

Although transient senescence may serve adaptive functions in wound healing and tumor suppression, accumulation of senescent cells over time contributes substantially to chronic inflammation.¹² Although senescent cells no longer divide, they sustain a vigorous secretory program—the SASP—through which they release inflammatory mediators, matrix-degrading proteases, chemokines, and mitogenic signals into the surrounding tissue microenvironment.¹³

The relationship between senescence and immunity is reciprocal. Within the adaptive compartment, senescent T-cell populations may contribute to reduced proliferative reserve and altered cytokine signaling, with context-dependent protective and detrimental effects in aging tissues.¹⁴ Age-related defects in cytotoxic lymphocyte activity, macrophage phagocytosis, and efferocytosis may therefore permit senescent-cell persistence, increasing SASP exposure and reinforcing chronic inflammatory tone.¹⁵

The SASP exerts profound paracrine effects on surrounding tissues. Pro-inflammatory mediators released by senescent cells induce neighboring cellular dysfunction, propagate senescence into adjacent microenvironments, and amplify inflammatory signaling across tissues. IL-6 and IL-1 β appear particularly important in sustaining SASP-related inflammatory loops.

Importantly, senescence is not restricted to a single tissue type. Senescent endothelial cells impair vascular homeostasis; senescent adipocytes promote metabolic inflammation; senescent chondrocytes contribute to osteoarticular degeneration; and senescent glial cells may participate in neuroinflammatory processes. Consequently, cellular senescence acts as a distributed inflammatory amplifier operating across organ systems.¹⁶

The relationship between senescence and inflammation is also bidirectional. Chronic inflammatory exposure accelerates cellular senescence through oxidative damage and genomic instability, while senescent cells themselves perpetuate inflammation through SASP signaling. This self-reinforcing cycle may represent one of the fundamental engines driving biological aging.¹⁷

Recent translational interest has focused on senolytic therapies that selectively eliminate senescent cells.¹⁸ Although still investigational, such approaches highlight the growing recognition that senescence may constitute a therapeutically modifiable contributor to inflammaging rather than an inevitable consequence of aging alone. Figure 2 depicts details on senescence, inflammation, and immunity.

2.3. Mitochondrial dysfunction and oxidative stress

Mitochondrial dysfunction occupies a central position within the biological architecture of inflammaging. Mitochondria regulate energy production, redox signaling, apoptosis, calcium homeostasis, and innate immune activation. Age-associated mitochondrial decline, therefore, exerts wide-ranging effects across multiple physiological systems.

Defective oxidative phosphorylation increases reactive oxygen species (ROS) production, contributing to oxidative injury affecting proteins, lipids, and nucleic acids. Elevated ROS levels also activate pro-inflammatory

cascades via NF- κ B signaling and inflammasome activation. Mitochondrial dysfunction, therefore, serves not merely as a marker of cellular damage but as an active mediator of inflammatory propagation. Particularly important is the relationship between mitochondrial injury and the NOD-like receptor family pyrin domain-containing 3 inflammasome. Damaged mitochondria release mitochondrial DNA and ROS, which can activate inflammasome complexes within innate immune cells. Inflammasome activation subsequently promotes maturation of IL-1 β and IL-18, thereby intensifying inflammatory signaling.¹⁹ Mitochondrial quality control mechanisms also deteriorate with age. Impaired mitophagy permits accumulation of dysfunctional mitochondria, further amplifying oxidative stress and inflammatory activation. Simultaneously, reduced mitochondrial biogenesis limits cellular adaptive capacity under conditions of metabolic stress.²⁰ These processes appear especially relevant within metabolically active tissues such as skeletal muscle, myocardium, and neural tissue. Chronic mitochondrial dysfunction contributes to sarcopenia, insulin resistance, endothelial dysfunction, and

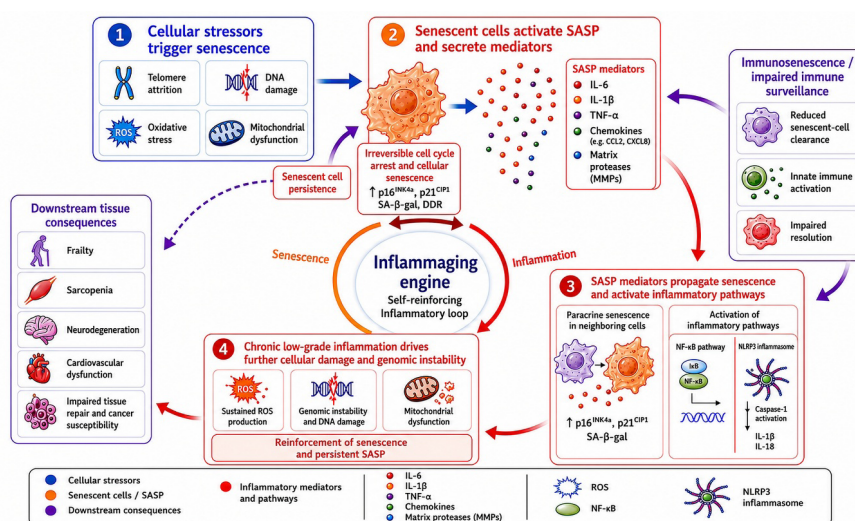


Figure 2. Immune surveillance-senescence-SASP-inflammation feedback loop in inflammaging. Cellular stressors, including telomere attrition, DNA damage, oxidative stress, and mitochondrial dysfunction, induce irreversible cell-cycle arrest and cellular senescence. Senescent cells develop the senescence-associated secretory phenotype (SASP), characterized by the release of pro-inflammatory cytokines, chemokines, and matrix-remodeling enzymes, including IL-6, IL-1 β , TNF- α , and matrix metalloproteinases. Persistent SASP signaling promotes paracrine senescence in neighboring cells and activates inflammatory pathways, including NF- κ B and the NLRP3 inflammasome. SASP mediators also reshape local immune activity, favoring persistent innate immune activation and impaired inflammatory resolution. Conversely, immunosenescence may reduce immune surveillance and senescent-cell clearance, allowing senescent cells and their secretory program to persist within tissues. Chronic low-grade inflammation further amplifies oxidative injury, genomic instability, and mitochondrial dysfunction, thereby reinforcing senescence and sustaining a self-perpetuating inflammaging loop. Downstream consequences include frailty, sarcopenia, neurodegeneration, cardiovascular dysfunction, impaired tissue repair, and increased cancer susceptibility. Abbreviations: IL: Interleukin; MMP: Matrix metalloproteinase; NF: Nuclear factor; NLRP3: NOD-like receptor family pyrin domain-containing 3; ROS: Reactive oxygen species; SASP: Senescence-associated secretory phenotype; TNF: Tumor necrosis factor.

neurodegenerative vulnerability, thereby linking cellular bioenergetics directly to systemic aging phenotypes.

Importantly, mitochondrial dysfunction interacts closely with lifestyle factors, including physical inactivity, obesity, poor sleep, and dietary quality. Such interactions reinforce the concept that inflammaging arises from the convergence of intrinsic aging mechanisms and environmental exposures rather than from genetically predetermined decline alone.²¹

2.4. Epigenetic regulation of inflammatory aging

Epigenetic remodeling represents an additional mechanistic layer contributing to inflammaging. DNA methylation, histone modification, chromatin remodeling, and non-coding RNA regulation collectively influence inflammatory gene expression patterns during cellular senescence and aging.²²

Age-associated epigenetic drift alters transcriptional regulation of cytokine pathways, oxidative stress responses, and innate immune signaling. Persistent activation of NF- κ B-related transcriptional programs appears particularly important in sustaining chronic inflammatory phenotypes. Similarly, altered signal transducer and activator of transcription signaling contributes to dysregulated cytokine production and impaired immune resolution.

Epigenetic mechanisms additionally mediate interactions between environmental exposures and biological aging. Diet, smoking, pollution, psychosocial stress, physical activity, and sleep quality may all influence inflammatory gene expression through epigenetic pathways. Consequently, inflammaging reflects not only intrinsic biological aging but also cumulative environmental imprinting across the lifespan.²³ Emerging evidence suggests that some epigenetic alterations may be reversible. This possibility has generated considerable interest in interventions targeting chromatin regulation, metabolic pathways, and inflammatory transcriptional programs as potential anti-aging strategies.

2.5. Cytokine network architecture

In inflammaging, cytokine elevation should not be interpreted as inflammation occurring independently of immune aging. Rather, it reflects a shift from tightly regulated immune activation and resolution toward persistent innate signaling, impaired adaptive control, and incomplete termination of tissue inflammatory responses. Inflammaging can be considered a paradoxical pattern of innate immune remodeling, in which expanded and cytokine-active cell populations coexist with impaired effector function and defective inflammatory resolution.²⁴

Interleukin-6 occupies a particularly central role within inflammaging biology. Elevated IL-6 concentrations correlate strongly with frailty, sarcopenia, cardiovascular disease, disability, and mortality.²⁵ Importantly, IL-6 exerts both pro-inflammatory and adaptive functions depending upon signaling context, tissue origin, and receptor dynamics. TNF- α contributes to endothelial dysfunction, insulin resistance, mitochondrial impairment, and tissue catabolism, whereas IL-1 β plays a critical role in inflammasome-mediated inflammatory amplification. Persistent activation of these cytokine networks progressively alters vascular integrity, musculoskeletal homeostasis, and neuroimmune communication.²⁶

The systemic consequences of chronic cytokine exposure become particularly evident in frailty syndromes. Elevated inflammatory biomarkers correlate with reduced muscle strength, impaired mobility, diminished intrinsic capacity, and loss of physiological resilience.²⁷ Chronic low-grade inflammation may therefore contribute mechanistically to frailty rather than merely accompany it. Increasingly sophisticated analytical approaches now emphasize composite inflammatory signatures rather than isolated biomarkers. Machine-learning models integrating cytokines, metabolic markers, microbiome-derived metabolites, and physiological variables may provide more accurate representations of biological aging trajectories and disease risk.

Ultimately, inflammaging appears to emerge from cumulative dysregulation across multiple interconnected systems rather than from singular inflammatory pathways. This systems-level perspective may prove essential for developing more effective preventive and therapeutic strategies in aging medicine.

3. Tissue interfaces: Where chronic inflammation acquires clinical form

If inflammaging begins as a disturbance in immune regulation, it becomes clinically meaningful only when it is translated through tissues. Aging tissues are not passive targets of inflammatory mediators; they are active participants in a distributed biological conversation. Adipose tissue, liver, skeletal muscle, vascular endothelium, kidney, brain, gut, and synovium each interpret inflammatory signals according to their own structural constraints, metabolic demands, and regenerative capacity. This is why chronic low-grade inflammation does not produce a single disease but a spectrum of phenotypes: sarcopenia in muscle, accelerated brain aging in neural tissue, vascular complications in diabetes, myocardial fibrosis, dysbiosis in the gut, and functional decline in frailty syndromes.²⁸

This tissue-level perspective is essential. It prevents the reduction of inflammaging to a circulating-cytokine problem and instead frames it as a disturbance in biological communication.

In this view, inflammation is not simply “present” or “absent”; it is spatially organized, temporally dynamic, and biologically interpreted. Circulating IL-6 should be interpreted as an integrated systemic signal rather than as a tissue-specific readout. Recent blood-based epigenomic evidence links circulating IL-6 to heterogeneous immunometabolic and inflammatory regulatory networks, indicating that its biological significance extends beyond a single inflammatory pathway. Attribution of a given circulating IL-6 concentration to visceral adipose tissue, skeletal muscle, liver, vascular tissue, or the intestine, however, requires tissue-specific mechanistic evidence.²⁹ This point is illustrated by large-scale metabolic-inflammatory clustering studies. In a UK Biobank analysis of nearly 400,000 participants, integrated metabolic and inflammatory phenotyping identified distinct risk profiles for digestive diseases, with metabolomic signatures mediating part of the association between inflammatory-metabolic clusters and disease susceptibility.³⁰ This finding is conceptually important because it demonstrates that inflammation becomes more informative when embedded within a metabolic context. The biomarker alone is not the disease; the network in which it operates is the disease substrate.

3.1. Adipose tissue: The immunometabolic amplifier

Adipose tissue is a central anatomical mediator of inflammaging. In younger individuals, it operates as an adaptive energy-buffering compartment, whereas aging and chronic nutritional surplus drive structural and immunological remodeling.

Visceral adiposity expands, adipocytes hypertrophy, local hypoxia develops, macrophages accumulate, and adipokine secretion becomes dysregulated. The tissue gradually shifts from energy storage to inflammatory signaling.³¹ This transformation is particularly relevant in older adults, in whom excess adiposity often coexists with sarcopenia, insulin resistance, and vascular disease. Obesity in later life cannot be characterized by body mass index. The distribution, inflammatory activity, and cellular composition of adipose tissue are more relevant than mass alone. Visceral and ectopic fat depots behave as immunometabolic organs, secreting cytokines, chemokines, leptin, resistin, and other mediators that interact with vascular and metabolic systems.³²

The clinical implications are considerable. In elderly

populations, obesity-related inflammatory biomarkers are associated with cardiometabolic risk, and the coexistence of hypertension or diabetes appears to intensify this inflammatory phenotype.³³ This supports the concept of adipaging: the convergence of adipose dysfunction and biological aging into a shared inflammatory state. Adipose tissue does not merely accompany aging-related disease; it helps to organize it.

Adipose inflammation also provides a mechanistic bridge between metabolic disease and vascular injury. Insulin resistance increases lipolysis, free fatty acid flux, endothelial stress, and oxidative injury. Inflammatory cytokines further impair insulin receptor signaling and promote endothelial dysfunction. A reciprocal loop is established: metabolic dysfunction produces inflammation, and inflammation worsens metabolic dysfunction. This loop is not confined to adipose tissue but extends to the liver, myocardium, skeletal muscle, and brain.³⁴

The concept of diabetes captures this convergence particularly well. In older cardiovascular patients, obesity and type 2 diabetes combine to promote myocardial inflammation, epicardial adipose expansion, fibrosis, neurohumoral activation, and cardiometabolic remodeling.³⁵

Epicardial fat is especially instructive because it lacks a fascial barrier separating it from myocardium. Its inflammatory secretome can directly act on adjacent coronary arteries and cardiac muscle, serving as a local interface between systemic metabolism and structural heart disease.

3.2. Liver, MASLD, and brain aging: Metabolic inflammation becomes neurological risk

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become one of the most relevant examples of how low-grade inflammation links metabolic organs to distant systems. The liver sits at the crossroads of nutrient flux, lipid handling, insulin signaling, immune surveillance, and the production of inflammatory mediators. When hepatic metabolism becomes disordered, the liver becomes not only a metabolic victim but also an inflammatory broadcaster.

In population-based imaging studies, MASLD has been associated with accelerated brain aging, even in middle-aged adults and in individuals without clinically apparent neurological disease. Low-grade systemic inflammation partially mediated this association, suggesting that hepatic-metabolic dysfunction may influence brain structure through inflammatory pathways.³⁶ This finding strengthens the argument that inflammaging is not a

compartmentalized process. A liver phenotype may become a brain phenotype because inflammation provides the systemic communication channel.

The mechanism is likely multifactorial. Hepatic steatosis promotes insulin resistance, dyslipidemia, endothelial dysfunction, and the release of pro-inflammatory mediators. These processes can impair cerebral microvasculature, alter blood–brain barrier integrity, and contribute to neuroinflammatory activation. Brain aging, therefore, may partly reflect the cumulative inflammatory burden of peripheral metabolic organs. This does not mean that inflammation is the only mediator linking MASLD to brain aging.³⁷ Other mechanisms, including vascular stiffness, glycemic variability, lipid toxicity, and mitochondrial dysfunction, almost certainly also contribute. However, the mediation signal is important because it identifies inflammation as a measurable and potentially modifiable pathway within a broader metabolic-neurological axis.

3.3. The gut–immune axis: Dysbiosis, barrier failure, and systemic propagation

The gut is not merely a digestive organ; it is an immune organ, a metabolic organ, and a microbial ecosystem. Its relevance to inflammaging arises from three interdependent functions: maintaining epithelial barrier integrity, regulating host–microbial immune tolerance, and producing metabolites that shape systemic physiology. Aging disrupts all three.³⁸

Gut dysbiosis in older adults is characterized by reduced microbial diversity, loss of beneficial butyrate-producing taxa, enrichment of pathobionts, and altered microbial metabolism. These changes may increase epithelial permeability, allowing microbial products such as lipopolysaccharide to enter the circulation and activate innate immune pathways. The result is a form of metabolic endotoxemia that can contribute to chronic low-grade inflammation.³⁹

Diet strongly shapes this axis. In older American men, inflammatory and insulinemic dietary patterns were associated with gut microbial composition and circulating metabolic biomarkers, suggesting that diet influences inflammation partly through microbial ecology.⁴⁰ This is clinically important because it links a modifiable exposure—dietary pattern—to a biological interface that regulates systemic inflammation.

The gut–immune axis is also relevant to hypertension. In elderly Chinese patients with hypertension, gut microbiota dysbiosis was associated with systemic inflammatory features, including elevated pro-inflammatory cytokines and altered abundance of taxa linked to short-chain fatty acid production.⁴¹ These findings suggest that vascular

aging may be partly shaped by microbial-inflammatory interactions. Hypertension, traditionally framed as a hemodynamic disorder, may also represent an immune-metabolic-microbial phenotype. The therapeutic implication is not simply probiotic prescription. Microbiome interventions are highly context-dependent. The same intervention may produce different effects according to baseline diet, medication exposure, host genetics, comorbidity, and existing microbial structure. Future microbiome-directed strategies should include phenotyping rather than generic supplementation.

3.4. Skeletal muscle: Inflammation, sarcopenia, and physical reserve

Skeletal muscle is both a target and a regulator of inflammation. It represents a large endocrine organ capable of producing myokines, regulating glucose disposal, and influencing systemic metabolism. With aging, muscle mass and strength decline, but this process is not simply mechanical wasting. Chronic inflammation contributes to impaired proteostasis, mitochondrial dysfunction, anabolic resistance, and reduced regenerative capacity. Sarcopenia is therefore not only a musculoskeletal condition; it is an inflammatory-metabolic syndrome.⁴²

Dietary inflammatory patterns, reduced physical activity, oxidative stress, and cytokine excess converge on muscle tissue, impairing contractile function and structural resilience. In older Polish adults, a higher dietary inflammatory index was associated with sarcopenia, slower gait speed, shorter six-minute walk distance, and higher levels of IL-1 β , IL-6, TNF- α , CRP, and cell-free DNA.⁴³

The relevance of cell-free DNA is particularly interesting. It suggests that inflammatory assessment in sarcopenia may eventually extend beyond conventional cytokines to damage-associated molecular signals reflecting tissue stress. Such markers may better capture the interface between cellular injury and systemic inflammation.

High-sensitivity CRP has also been associated with reduced muscle strength in large population studies. Among Korean adults, elevated high-sensitivity CRP (hsCRP) was independently associated with lower handgrip strength, particularly among middle-aged women and older adults.⁴⁴ Although observational, these findings support the concept that low-grade inflammation contributes to functional decline before severe disability becomes clinically apparent.

In patients undergoing peritoneal dialysis, sustained CRP elevation was associated with loss of lean tissue over time, despite similar baseline body composition.⁴⁵ This provides a clinically powerful example of inflammation as a catabolic force. The inflammatory state did not

merely correlate with poor health; it predicted structural deterioration of muscle compartments in a vulnerable population.

3.5. Frailty and intrinsic capacity: Inflammation as loss of resilience

Frailty is one of the most clinically important expressions of inflammaging because it converts molecular dysregulation into observable vulnerability. It is not defined by a single organ failure but by reduced reserve across systems. This makes frailty an ideal clinical model for understanding inflammaging as a system failure.

Intrinsic capacity offers a complementary framework. Rather than focusing only on deficits, it captures locomotion, cognition, vitality, psychological function, and sensory capacity. In community-dwelling octogenarians, intrinsic capacity–frailty phenotypes showed a biological gradient of subclinical inflammation, with CRP, IL-6, and TNF- α increasing from robust to frail phenotypes.⁴⁶ Locomotion and vitality emerged as particularly inflammation-sensitive domains. This finding has conceptual importance. It suggests that inflammation maps not only onto disease categories but onto functional architecture. In other words, inflammatory burden may be better understood as a measure of declining resilience than as a disease-specific marker. This shift is crucial for geriatric medicine, where the goal is not merely disease control but preservation of function.

Frailty also illustrates the limitation of single-organ medicine. A patient may have modest elevations of inflammatory markers, mild sarcopenia, early cognitive slowing, reduced gait speed, and subclinical vascular disease. None alone may appear dramatic. Together, they define a vulnerable biological state. Inflammaging provides a framework for understanding that state as an integrated rather than fragmented phenomenon.⁴⁷

3.6. Neuroinflammation and brain aging

The nervous system is highly sensitive to inflammatory signaling. Although the brain has long been described as immunologically privileged, it is now clear that systemic inflammation can influence neural function through endothelial activation, increased blood–brain barrier permeability, microglial priming, altered neurotransmitter metabolism, and vascular dysfunction.

Brain aging studies increasingly use the imaging-derived brain-age gap as a surrogate for neurobiological aging. Poor sleep health has been associated with older brain age, and systemic inflammation mediates part of this association.⁴⁸ This reinforces the idea that behavioral

exposures, inflammatory biology, and neural aging are linked through measurable pathways.

Sleep is particularly relevant because it regulates immune activity, glymphatic clearance, neuroendocrine rhythms, and metabolic homeostasis. Chronic sleep disruption may therefore amplify inflammaging not merely by raising inflammatory markers but by impairing the nocturnal repair systems that ordinarily maintain neural resilience.

Parkinson's disease offers another example of selective neuroimmune vulnerability. In a perioperative cytokine study, patients with Parkinson's disease showed evidence compatible with chronic low-grade inflammation, although acute perioperative cytokine responses were not globally amplified compared to controls.⁴⁹ This distinction is important, as inflammaging is not always an exaggerated response; in some contexts, it may involve selective immune dysregulation, exhaustion, or impaired adaptability.

Long COVID further complicates the inflammatory model. In longitudinal biomarker studies, an early phase of low-grade inflammation in long COVID appeared to shift toward reduced pro-inflammatory biomarkers later, suggesting possible immune suppression or exhaustion rather than persistent hyperinflammation alone.⁵⁰ This finding is important because it challenges a simplistic model that equates chronic disease with continuously elevated cytokine levels. Instead, it suggests that dynamic dysregulation may be more informative than static elevation.

3.7. Cardiovascular disease: Inflammation as risk modifier and tissue driver

Cardiovascular disease remains one of the strongest clinical domains for studying chronic low-grade inflammation. Atherosclerosis is fundamentally an inflammatory process, involving endothelial activation, leukocyte recruitment, lipid oxidation, plaque remodeling, and thrombo-inflammatory signaling. However, recent evidence suggests that inflammation may not only contribute to baseline risk but also modify the pathogenicity of specific lipid-related factors.

In a secondary prevention cohort, IL-6 modified the association between lipoprotein(a), oxidized phospholipids, and cardiovascular risk, whereas hsCRP did not.⁵¹ This distinction is important. It suggests that inflammatory biomarkers are not interchangeable and that IL-6 may capture risk biology not reflected by CRP alone.

Peripheral artery disease and chronic limb-threatening ischemia offer another example of inflammatory risk

stratification. In patients undergoing revascularization, higher comorbidity-polypharmacy scores were associated with increasing neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index.⁵² Such markers are imperfect but clinically accessible, making them attractive candidates for pragmatic inflammatory phenotyping in high-risk vascular populations.

Subclinical myocardial inflammation also appears relevant in metabolic cardiac disease. In hypertrophic cardiomyopathy, abnormal glucose metabolism was associated with myocardial fibrosis and imaging features consistent with subclinical inflammation on cardiac magnetic resonance.⁵³ These findings suggest that glycemic status can shape myocardial tissue biology through inflammatory and fibrotic pathways even before overt clinical decompensation.

3.8. Depression, metabolic dysfunction, and the neurovascular interface

Depression in older adults increasingly appears to involve inflammatory, metabolic, vascular, and neurodegenerative components.⁵⁴ Yet the relationship is not straightforward. In a large prospective cohort examining type 2 diabetes and incident depressive symptoms, microvascular dysfunction, neurodegeneration, advanced glycation end products, and arterial stiffness partly mediated the association, whereas low-grade inflammation did not independently mediate it.⁵⁵ This finding indicates that inflammation is not always the dominant pathway and should not be invoked indiscriminately. In some disease relationships, vascular and neurodegenerative mechanisms may carry more explanatory weight than circulating inflammatory biomarkers.

In contrast, in cognitively healthy older adults, insulin resistance showed a sex-specific association with depressive symptoms, with vascular endothelial growth factor emerging as a potential mediator in women.⁵⁶ This suggests that inflammatory-metabolic signatures may differ by sex, vascular biology, and neuroendocrine context. Precision inflammaging should therefore require stratification by biological subgroup rather than broad disease labels.

3.9. Subclinical inflammation and imaging phenotypes

One of the most important trends in current inflammaging research is the movement from circulating markers toward imaging-defined inflammatory phenotypes. Subclinical inflammation may be spatially localized and clinically silent, yet biologically consequential. In patients with giant cell arteritis, fluorodeoxyglucose positron emission

tomography/computed tomography detected subclinical optic nerve inflammation, even in those without visual symptoms.⁵⁷ Although this disease differs from low-grade inflammaging, the principle is relevant: inflammatory activity may exist below the threshold of clinical detection while still carrying prognostic implications.

The future of inflammaging research will likely integrate circulating biomarkers, imaging, omics, and functional outcomes. A single blood test cannot fully capture inflammatory geography.

Conversely, imaging without systemic biomarker context may miss the organism-wide inflammatory state. The most informative models will combine both.

4. Synthesis: From tissue injury to distributed disease

Inflammaging should not be understood solely as a circulating cytokine state, but as a distributed process arising from interacting tissue-level sources. Visceral adipose tissue can convert metabolic excess into pro-inflammatory signaling. Age-related gut dysbiosis and impaired intestinal barrier integrity can facilitate bacterial translocation and immune activation. In skeletal muscle, chronic inflammation contributes to loss of mass, reduced strength, and sarcopenia.⁵⁸

Metabolic liver dysfunction, including nonalcoholic fatty liver disease, is linked to cognitive impairment and neurodegenerative processes through insulin resistance, inflammatory signaling, and vascular mechanisms. Metabolic and inflammatory disturbances are associated with endothelial dysfunction, atherosclerosis, and cerebrovascular abnormalities. In the brain, systemic inflammatory signaling can promote blood-brain barrier dysfunction and microglial activation.⁵⁹

This framework helps explain why the same inflammatory mediator may be associated with multiple diseases without implying that all diseases are the same. IL-6 in vascular disease, CRP in muscle weakness, the dietary inflammatory index in sarcopenia, and microbiome dysbiosis in hypertension represent different expressions of a shared principle: inflammation becomes pathogenic through context.

The clinical future of inflammaging will therefore depend on mapping the inflammatory context: Who is inflamed? Where is the signal generated? Which tissue is interpreting it? Is the inflammatory state adaptive, maladaptive, exhausted, or compensatory? Does it predict disease, mediate disease, or merely accompany disease? These questions move the field beyond biomarker enumeration toward pathophysiological interpretation.

5. Modifying inflammaging: Interventions, translation, and future directions

The clinical relevance of inflammaging depends not only on its ability to explain disease, but also on whether its determinants can be modified. Current evidence indicates that chronic low-grade inflammation is amenable to therapeutic modulation, although it does not represent a single biological target. Rather, inflammaging reflects an interconnected process influenced by physical activity, dietary patterns, adiposity, sleep, psychological stress, and mechanisms related to the gut microbiome. Accordingly, its management is more amenable through integrated, multidomain strategies than through any single intervention or biomarker threshold.⁶⁰ This point is particularly important because the history of anti-inflammatory medicine has often been disease-specific.

Rheumatology, dermatology, gastroenterology, and cardiovascular medicine have all developed targeted approaches for overt inflammation. Inflammaging, in contrast, is usually subclinical, diffuse, and entangled with aging biology. Its modulation must therefore be conceived less as suppression and more as recalibration. The goal is not to eliminate inflammation, which remains indispensable for defense and repair, but to restore the temporal and spatial precision of inflammatory responses.

The therapeutic framework that follows is therefore organized around four principles: first, interventions should restore physiological resilience rather than merely reduce biomarkers; second, the same intervention may have different effects depending on the baseline inflammatory phenotype; third, multimodal strategies are likely to outperform isolated interventions; and fourth, future clinical translation will require composite biomarkers capable of tracking inflammatory trajectories rather than relying on single measurements.

5.1. Exercise as an anti-inflammatory signal

Exercise is one of the best non-pharmacological interventions for inflammaging because it engages nearly every relevant biological interface: skeletal muscle, adipose tissue, endothelium, mitochondria, neuroendocrine regulation, and immune cell function. Unlike pharmacological suppression, exercise produces controlled physiological stress followed by adaptive repair. Inflammatory signaling during and after exercise is therefore not inherently pathological; it is part of the adaptive program through which tissues remodel, mitochondria are renewed, and immune responses are recalibrated.⁶¹

Meta-analytic evidence supports this biological

plausibility. In older adults, resistance training has been shown across randomized trials to reduce CRP and TNF- α , with a trend toward lower IL-6 involving individuals aged 60 years or older.⁶² The clinical implication is not merely that exercise lowers inflammatory markers, but that muscle contraction can shift systemic inflammatory tone through repeated adaptive signaling.

The anti-inflammatory effects of exercise are mediated through several converging pathways. Improved muscle mass increases glucose disposal and reduces insulin resistance. Reduced visceral adiposity decreases adipose-derived cytokine production. Enhanced mitochondrial function reduces oxidative stress. Repeated mechanical loading improves muscle quality, vascular function, and endothelial nitric oxide bioavailability. Myokines released during contraction may further exert anti-inflammatory effects by promoting metabolic flexibility and immune regulation. However, the interaction between exercise and aging is not uniformly favorable. Older muscle may recover more slowly from exercise-induced damage, partly because of chronic low-grade inflammation, extracellular matrix stiffening, satellite-cell dysfunction, and mitochondrial impairment.⁶³ This observation is clinically important: the same exercise stimulus that is adaptive in younger tissue may be excessive or inefficient in older tissue unless appropriately prescribed. Inflammation, therefore, modifies not only disease risk but also treatment response. Combined interventions may offer additional advantages. A recent trial in healthy older adults found that resistance training combined with minimal high-intensity interval training improved lean mass, strength, and aerobic capacity, and attenuated selected acute exercise-induced inflammatory responses; polyphenol supplementation alone had more limited effects.⁶⁴ This pattern reinforces the primacy of structured physical activity as a systems-level intervention, while suggesting that nutritional adjuncts may be supportive rather than sufficient.

The practical message is clear. Exercise should not be framed as an optional lifestyle recommendation appended to pharmacological care. In inflammaging, exercise is a biological therapy acting across immune, metabolic, vascular, and musculoskeletal interfaces. The challenge is to tailor the dose, mode, progression, and recovery to the individual's inflammatory and functional phenotype.

5.2. Nutrition, protein, and dietary inflammatory load

Nutrition is the second major modifiable axis of inflammaging. Diet shapes inflammatory biology through energy balance, adipose tissue mass, micronutrient sufficiency, oxidative stress, glycemic variability, lipid

metabolism, and microbiome composition. The clinical literature is heterogeneous, but the evidence is consistent: dietary patterns that improve metabolic health and microbial ecology tend to attenuate the inflammatory burden.

Systematic review evidence indicates that exercise and dietary supplementation in older adults may reduce pro-inflammatory cytokines, although the magnitude and consistency of effects vary across interventions and study designs.⁶⁵ This heterogeneity should not be viewed as a failure. It reflects the biological heterogeneity of inflammaging. A supplement may have little measurable effect in a well-nourished older adult with low baseline inflammation, but may be meaningful in a frail, sarcopenic, metabolically stressed patient.

Protein supplementation is especially relevant because muscle decline is one of the main clinical expressions of inflammaging. A meta-analysis of randomized trials found that whey protein reduced circulating IL-6 and soy protein reduced TNF- α , with stronger effects in participants with sarcopenia or pre-frailty.⁶⁶ These findings support the concept that nutrition can modulate inflammation through muscle proteostasis, not only through classical immune pathways.

Dietary inflammatory load also matters. Diets rich in ultra-processed foods, refined carbohydrates, and saturated fats and low in fiber may promote metabolic endotoxemia, dysbiosis, oxidative stress, and adipose inflammation. Conversely, diets rich in vegetables, legumes, whole grains, unsaturated fats, fermented foods, and polyphenol-containing foods may reduce inflammatory tone through both metabolic and microbiome-mediated mechanisms. However, not all anti-inflammatory nutritional interventions translate into positive outcomes in clinical trials. In postmenopausal women with overweight or obesity, high-dose green tea extract taken for one year did not significantly reduce CRP, IL-6, or TNF- α , and the catechol-O-methyltransferase genotype did not modify the effect.⁶⁷ This negative result is useful because it reminds us that isolated bioactive compounds may not reproduce the effects of dietary patterns. The organism responds to food architecture, timing, energy balance, microbial fermentation, and tissue state—not merely to single molecules. Traditional or botanical interventions also remain of interest, although evidence quality varies. In metabolic syndrome, Huanglian Jiedu decoction added to lifestyle guidance was associated with reductions in body weight, metabolic indices, IL-6, IL-17A, and TNF- α over three months.⁶⁸ Such studies should be interpreted cautiously because reproducibility, standardization, and generalizability remain important concerns; nonetheless,

they illustrate the broader principle that metabolic inflammation can be pharmacologically or nutraceutically modulated.

5.3. Microbiome-directed interventions

The gut microbiome is an attractive target for inflammaging because it is modifiable, mechanistically plausible, and linked to immune regulation. However, microbiome intervention remains less mature than the enthusiasm surrounding it. The field must distinguish between three levels of claim: association, modulation, and clinical benefit. Many studies have demonstrated association, whereas fewer have demonstrated durable microbial modulation, and fewer still have demonstrated meaningful clinical outcomes.

A randomized, double-blind, placebo-controlled trial of *Lactiplantibacillus plantarum* HEAL9 in older adults with chronic low-grade inflammation found modest effects, including reduced fecal calprotectin, a trend toward lower serum CRP, and possible cognitive signals that did not reach statistical significance.⁶⁹ This type of result is probably representative of the field: microbiome interventions may work, but the effects are often modest, strain-specific, and dependent on baseline inflammatory state.

Microbiome-directed therapy should therefore not be reduced to generic probiotic use. More plausible future strategies include targeted prebiotics, resistant starches, fermented foods, synbiotics, postbiotics, microbiome-informed dietary counseling, and perhaps personalized microbial restoration. The key is ecological rather than additive thinking. A probiotic strain introduced into an unfavorable dietary and microbial ecosystem may fail to engraft or function. Conversely, dietary fiber and substrate availability may allow beneficial taxa to expand without the need for exogenous organisms.

Microbial metabolites may ultimately be more clinically informative than taxonomy alone. Butyrate, propionate, bile acid derivatives, indoles, and other metabolites regulate epithelial integrity, immune tolerance, metabolic signaling, and neuroimmune communication. Future trials should therefore measure not only microbial composition but also functional metabolic output.

5.4. Sleep, stress, and neuroendocrine modulation

Inflammaging is often discussed in immune and metabolic terms, but neuroendocrine regulation is equally central. Sleep, circadian rhythm, cortisol dynamics, sympathetic tone, and psychological stress shape inflammatory signaling. This is clinically relevant because older adults frequently experience fragmented sleep, reduced circadian

amplitude, social isolation, fear of falling, pain, and multimorbidity-related stress.

Poor sleep health has already been linked to older brain age, partly through systemic inflammation. The translational implication is that sleep may be a modifiable inflammatory intervention rather than merely a symptom domain. Sleep interventions could plausibly reduce neuroinflammatory and cardiometabolic risk by restoring circadian immune regulation, improving glymphatic clearance, and reducing neuroendocrine stress.

The relationship between psychological stress and inflammation is complex. In the FEARFALL study, perceived control over falling was associated with cortisol dynamics, whereas inflammatory markers were more closely related to age and body mass index than to fear-related measures.⁷⁰ This distinction is important. Psychological factors may influence stress-system regulation even when they do not directly map onto CRP or IL-6. In clinical practice, this suggests that inflammatory resilience includes neuroendocrine adaptability, not only cytokine reduction.

Depression, frailty, and anxiety-like syndromes in older adults may therefore require integrated assessment. Treating depressive symptoms without assessing frailty, mobility, sleep, inflammation, and medication burden risks missing the systems-level nature of the problem. Conversely, improving physical function and perceived control may indirectly improve inflammatory and neuroendocrine regulation.

5.5. Pharmacological modulation: Promise and caution

Pharmacological modulation of inflammaging is conceptually appealing but clinically challenging. Targeted anti-cytokine therapies have transformed the treatment of autoimmune and autoinflammatory diseases, yet chronic low-grade inflammation differs fundamentally from overt inflammatory pathology. In older adults, indiscriminate immune suppression may increase infection risk, impair tissue repair, and worsen resilience. The goal should therefore be selective modulation of maladaptive inflammatory pathways while preserving host defense.

Anti-inflammatory interventions for depression illustrate both promise and uncertainty. A systematic review and meta-analysis in older adults found that anti-inflammatory interventions reduced depressive scores compared to placebo, with subgroup signals for omega-3 fatty acids and botanical or dietary interventions.⁷¹ However, heterogeneity was substantial, and baseline inflammatory status likely influenced response. This supports a biomarker-stratified model rather than

universal anti-inflammatory prescribing.

Senolytic and senomorphic strategies represent another frontier. By targeting senescent cells or modifying the SASP, these interventions aim upstream of cytokine excess. The theoretical advantage is that removing or reprogramming senescent inflammatory sources may produce broader effects than blocking a single cytokine. The risk is that senescence also serves protective functions in wound healing and tumor suppression. Timing, dose, tissue specificity, and patient selection will therefore be critical (Figure 3).

Cell-based approaches also raise translational questions. In older adults with Parkinson's disease and preserved kidney function, repeated allogeneic mesenchymal stem-cell infusions were associated with improved kidney-function measures in secondary analyses of a clinical trial.⁷² Although preliminary and disease-context-specific, such findings suggest that immunomodulatory cellular therapies may eventually intersect with inflammaging research. At present, however, they should be considered investigational rather than clinically established.

Figure 3 illustrates inflammaging as a dynamic systems-level process in which therapeutic interventions must reduce maladaptive chronic inflammation while preserving host defense, tissue repair, and physiological adaptation. Major therapeutic domains include targeted anti-cytokine therapies, senolytic and senomorphic strategies, nutritional and anti-inflammatory interventions, and cell-based immunomodulatory therapies. The central hub emphasizes the concept of selectively modulating maladaptive inflammation, balancing inflammatory suppression with maintenance of resilience and adaptive immune function. The potential benefits include reduced frailty, improved functional aging, and attenuation of the progression of multimorbidity, whereas excessive suppression may increase infection susceptibility, impair regeneration, and promote immune exhaustion. The right-side panel highlights the emerging paradigm of precision inflammaging, integrating biomarker-guided therapy, inflammatory phenotypes, and tissue-specific responses within personalized geroscience approaches.

5.6. Composite biomarkers and precision inflammation medicine

A recurring limitation throughout inflammaging research is the reliance on single biomarkers. CRP is useful, inexpensive, and prognostic, but it does not reflect the entire inflammatory state. IL-6 is informative, but not always superior. TNF- α and IL-1 β may be mechanistically important but difficult to interpret in isolation. Ratios such as neutrophil-to-lymphocyte and platelet-to-lymphocyte,

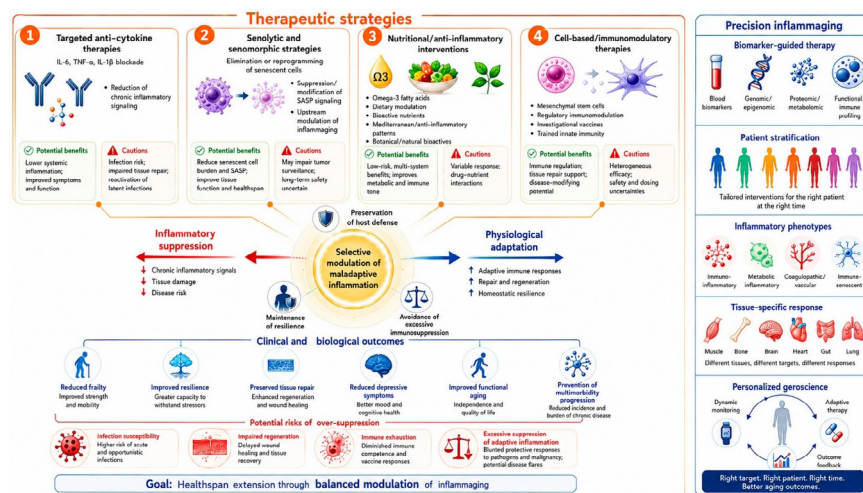


Figure 3. Pharmacological modulation of inflammaging as a balance between inflammatory control and preservation of biological resilience during aging. Abbreviations: IL: Interleukin; SASP: Senescence-associated secretory phenotype; TNF: Tumor necrosis factor.

as well as the systemic immune-inflammation index, are readily available but non-specific. The next phase of the field requires composite, context-aware biomarkers. Recent work on digital health and longevity has proposed inflammation-centered frameworks integrating hsCRP, IL-6, TNF- α , microbiome diversity, butyrate, insulin resistance, and lipid ratios into composite indices, such as the Longevity-Inflammation Index.⁷³ This approach is conceptually attractive because it recognizes that inflammaging is not purely immunological; it is immune-metabolic-microbial. However, composite indices must be validated rigorously. They require construct validity, predictive validity, responsiveness to intervention, population norms, and clinical interpretability.

A score that predicts mortality but cannot guide intervention may be epidemiologically useful but clinically limited. Conversely, a score that changes with lifestyle but does not predict outcomes may be motivational but not medically meaningful. Digital platforms may eventually permit repeated inflammatory phenotyping by combining laboratory biomarkers, wearable data, diet logs, sleep metrics, physical activity, and microbiome assessments. Yet this future must be approached carefully. Digital health can empower personalized prevention, but it can also generate noise, anxiety, and over-testing. Inflammation medicine must avoid becoming another domain of unregulated biomarker enthusiasm.

The ideal model would combine periodically validated biomarkers with clinically meaningful endpoints: gait speed, grip strength, cognitive performance, sleep quality, vascular events, metabolic control, and patient-centered

function. Inflammaging should not be treated as an abstract laboratory construct. It matters because it alters how people move, think, recover, and live.⁷⁴

6. Clinical trial design: Participant selection

A major obstacle in inflammaging research is trial heterogeneity. Numerous studies enroll broad older populations without sufficient inflammatory enrichment. If participants have low baseline inflammation, an intervention may appear ineffective despite biological plausibility. Future trials should stratify participants by inflammatory phenotype, metabolic state, frailty status, adiposity distribution, microbiome features, and functional reserve.

Trial endpoints should also be refined. CRP reduction alone is insufficient. More meaningful endpoints include preservation of muscle mass, improved intrinsic capacity, reduced frailty progression, delayed cognitive decline, improved vascular function, and fewer hospitalizations. In high-risk groups, hard outcomes may be feasible. In healthier populations, intermediate functional and biological endpoints will remain necessary.⁷⁵

Duration is another key issue. Inflammaging develops over years, whereas many intervention trials last weeks or months. Short trials may detect cytokine changes but miss structural and functional outcomes. Longer trials are more expensive and difficult, but they are essential if the field is to move beyond proof of mechanism.

Multimodal intervention trials may be particularly relevant. The biological architecture of inflammaging

suggests that exercise, diet, sleep, stress reduction, microbiome modulation, and medication optimization may act synergistically. Single interventions may produce modest effects because they target only one node in a network. Multidomain interventions, if well designed, may better restore system-level resilience.⁷⁶

7. A practical clinical framework

For clinicians, inflammaging should not be an excuse to order indiscriminate cytokine panels. A pragmatic approach begins with phenotype: Does the patient show frailty, sarcopenia, metabolic syndrome, recurrent infections, chronic pain, poor sleep, depression, functional decline, or accelerated vascular disease? Are there modifiable inflammatory drivers such as visceral adiposity, periodontal disease, sleep disruption, physical inactivity, uncontrolled diabetes, chronic kidney disease, or polypharmacy?⁷⁷

Initial assessment can reasonably include conventional markers such as hsCRP, complete full blood count with differential, albumin, glucose metabolism, lipid profile, renal function, and liver enzymes. More specialized markers may be appropriate in research settings or selected clinical contexts, but their routine use remains premature.

Management should prioritize interventions with broad benefit and low risk: progressive resistance and aerobic exercise, adequate protein intake, dietary quality, weight management where appropriate, sleep optimization, treatment of periodontal and chronic infectious sources, medication review, vaccination, and management of cardiometabolic disease. Pharmacological anti-inflammatory strategies should be reserved for defined indications or research protocols.⁷⁸

This approach does not trivialize inflammaging. Rather, it grounds the concept in actionable medicine. The clinician does not need to “treat IL-6”; they need to identify why the patient’s biological systems are generating persistent inflammatory tone and intervene at the relevant interface.

8. Future directions

The next generation of inflammaging research should move beyond biomarker association toward causal architecture. Several priorities are clear. First, longitudinal studies should identify inflammatory trajectories that precede disease, rather than merely measuring inflammation after disease is established. Second, mechanistic trials should test whether changing the inflammatory state changes functional outcomes. Third, tissue-specific and imaging-based approaches should be integrated with circulating biomarkers. Fourth, microbiome studies should emphasize function and metabolites rather than taxonomy alone.

Fifth, clinical trials should enrich for inflammatory phenotypes and use patient-centered endpoints.

Artificial intelligence and systems modeling may help, but only if grounded in biologically meaningful data. Machine-learning models can identify patterns, but they do not automatically explain mechanisms. The best use of computational tools will be to integrate multi-omic, physiological, behavioral, imaging, and clinical data into interpretable inflammatory phenotypes.

Equity is also important. Inflammaging is shaped by social determinants, including nutrition, pollution, infection burden, stress, work conditions, healthcare access, and the physical environment. A purely molecular account of inflammaging risks overlooking the social biology of inflammation. Chronic adversity is biologically embedded and contributes to inflammatory processes. Public health interventions may therefore be as anti-inflammatory as drugs.

9. Final integrative model: Inflammation as multiscale interface failure

Across the three phases of this review, a coherent model emerges. Inflammaging begins with immune remodeling, cellular senescence, mitochondrial dysfunction, epigenetic drift, and dysregulation of the cytokine network. It acquires clinical form through tissue interfaces: adipose tissue, liver, gut, skeletal muscle, vasculature, brain, kidney, and joints. It can be modified through interventions that restore adaptive signaling: movement, diet, sleep, microbial ecology, metabolic control, and selective pharmacology. The key conceptual shift is to view inflammation not as a linear pathway but as an architecture of communication. Biological systems require inflammatory signaling to detect danger, repair tissue, regulate metabolism, and adapt to stress.

Disease emerges when this signaling loses precision: when local signals become systemic, when acute responses fail to resolve, when repair becomes fibrosis, when defense becomes catabolism, and when adaptation becomes exhaustion. This phenomenon exemplifies multiscale interface failure. At the molecular scale, cytokine and inflammasome signaling become dysregulated. At the cellular scale, senescent and innate immune cells amplify inflammatory tone. At the tissue scale, adipose, gut, muscle, vascular, neural, and osteoarticular compartments interpret inflammation through local vulnerabilities. At the organismal scale, the result is frailty, multimorbidity, cognitive decline, and reduced resilience. Such a framework does not replace disease-specific medicine. Rather, it provides the connective tissue linking diseases that have too often been studied separately. It explains why a patient

with visceral adiposity, poor sleep, sarcopenia, depression, diabetes, and osteoarthritis should not be understood as a collection of unrelated diagnoses. The shared biology is not identical across all tissues, but the network is connected.

The translational promise of inflammaging lies in this integrative power. If measured wisely and treated contextually, chronic low-grade inflammation may become a practical organizing principle for preventive geroscience, multimorbidity care, and health span extension. The challenge now is to ensure that the field moves from elegant association to clinically meaningful intervention.

10. Conclusion

Inflammaging is no longer a marginal concept in aging biology. It is increasingly central to the understanding of chronic disease, frailty, neurodegeneration, cardiometabolic dysfunction, sarcopenia, and osteoarthritis. Yet its clinical value depends on conceptual discipline. Chronic low-grade inflammation should not be invoked as a universal explanation for every age-related phenomenon, nor should it be reduced to a single biomarker. It is a dynamic, contextual, and multiscale process. The evidence reviewed here supports a systems-level interpretation. A summary of these points is shown in Figure 4.

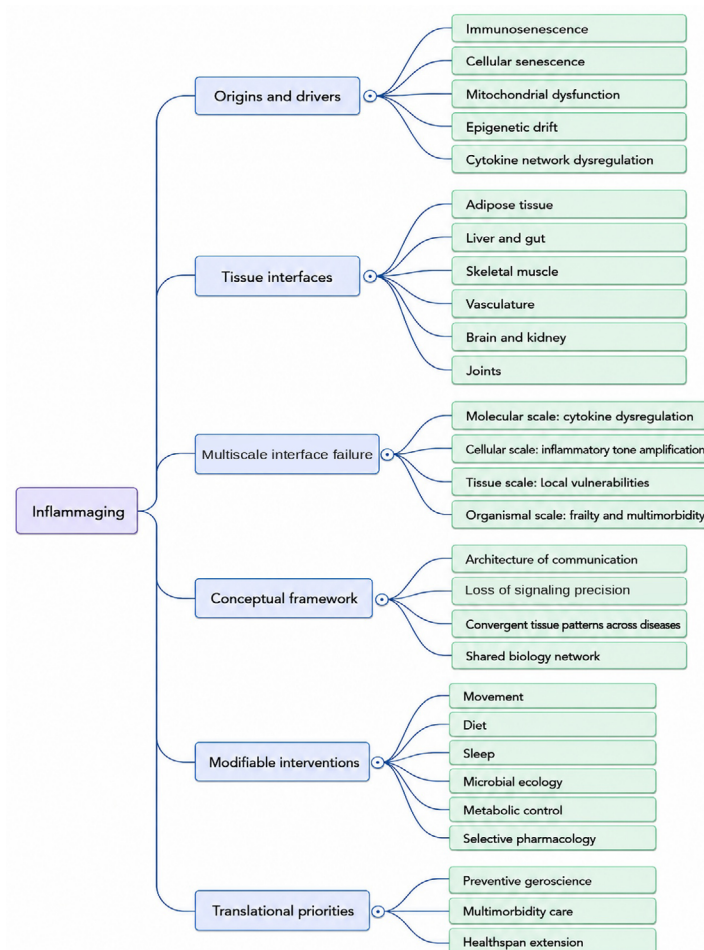


Figure 4. Inflammaging as a multiscale interface failure network. This conceptual framework illustrates inflammaging as a distributed systems-level process emerging from the interaction of biological aging mechanisms, tissue interfaces, and network-wide inflammatory dysregulation. Principal origins and drivers include immune remodeling, cellular senescence, mitochondrial dysfunction, epigenetic drift, and cytokine network instability. These processes propagate across multiple tissue interfaces, including adipose tissue, liver–gut interactions, skeletal muscle, vasculature, brain, kidney, and joints, thereby generating interconnected patterns of chronic low-grade inflammation. Inflammaging is conceptualized as a form of multiscale interface failure operating across molecular, cellular, tissue, and organismal levels, ultimately contributing to frailty, multimorbidity, and loss of physiological resilience. The framework further highlights inflammaging as a shared biological communication network characterized by impaired signaling precision and connective inflammatory architecture between chronic diseases. Potentially modifiable interventions include physical activity, diet, sleep optimization, microbial ecology modulation, metabolic control, and selective pharmacological approaches. Translational implications include preventive geroscience, integrated multimorbidity care, and extension of health span.

Inflammaging arises from the interaction of immune remodeling, cellular senescence, mitochondrial dysfunction, metabolic stress, microbiome dysbiosis, neuroendocrine regulation, and tissue injury. Its clinical expression depends on the interfaces through which these signals are interpreted. Its treatment will require interventions that restore resilience rather than merely suppress inflammation. The future of inflammaging medicine should not be defined solely by drugs or solely by lifestyle interventions. It should combine phenotyping, prevention, functional assessment, digital monitoring, targeted therapy, and public health. In that sense, inflammaging may not only be a mechanism of aging but also a language through which modern medicine learns to understand chronic disease as integrated biology.

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