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Molecular and cellular drivers of inflammaging: Uncovering the diverse mechanisms and interventions of inflammaging

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Abstract

Aging is accompanied by a persistent state of low-grade inflammation, widely referred to as “inflammaging”. Unlike acute inflammation, which is transient and protective, inflammaging represents a chronic, sterile, systemic process that accelerates tissue dysfunction and predisposes individuals to age-related diseases. Its origins are multifactorial, involving cellular senescence, impaired autophagy, mitochondrial dysfunction, dysregulated innate immune signaling, epigenetic alterations, and shifts in gut microbiota composition. These mechanisms converge to form a self-perpetuating cycle of inflammatory activation that compromises tissue homeostasis. The clinical consequences of inflammaging extend across diverse organ systems. It contributes to neurodegeneration through sustained neuroinflammation, promotes cardiovascular pathology by driving endothelial dysfunction and atherosclerosis, and accelerates pulmonary and musculoskeletal decline. Such broad involvement underscores its role as a unifying mechanism linking aging to chronic disease onset and progression. Therapeutic strategies have begun to target inflammaging directly. Senolytics eliminate senescent cells, while senomorphics suppress the senescence-associated secretory phenotype (SASP). Modulation of gut microbiota through dietary interventions, probiotics, or fecal microbiota transplantation restores microbial balance and reduces systemic inflammation. Lifestyle modifications, including caloric restriction, exercise, and improved sleep quality, further mitigate inflammatory burden and enhance resilience. This review

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synthesizes the current research progress on the molecular and cellular drivers of inflammaging and highlights emerging therapeutic approaches to alleviate chronic inflammation and extend healthy lifespan. It aims to provide a comprehensive framework for understanding inflammaging and deepen our understanding of inflammatory mechanisms, which will facilitate early detection, personalized treatment, and efficacy monitoring.

KEYWORDS

Inflammaging; Aging; Senescence-associated secretory phenotype; Interventions; Review

Introduction

Aging is a complex biological process characterized by the progressive deterioration of physiological integrity, leading to functional decline and increased vulnerability to disease. Among the many hallmarks of aging, chronic inflammation has emerged as a pivotal factor contributing to age-related functional decline. This phenomenon, often termed "inflammaging," describes a state of persistent, sterile, systemic inflammation that develops with age, independent of overt infection. Unlike acute inflammation, which is protective and self-limiting, inflammaging is subtle yet chronic, exerting long-term deleterious effects on tissue homeostasis and organismal health(1). Accumulating evidence indicates that inflammaging arises from multiple converging mechanisms, including immune cell senescence, impaired autophagy, mitochondrial dysfunction, defective resolution of inflammation, accumulation of damage-associated molecular patterns (DAMPs), and altered gut microbiota composition(2, 3). These mechanisms are intertwined and amplify each other, creating a self-sustaining loop of chronic inflammation.

The pathological consequences of inflammaging extend across multiple organ systems. Inflammaging has been implicated in the pathogenesis of numerous age-associated diseases, including cardiovascular disease, type 2 diabetes, neurodegeneration, osteoarthritis, and various cancers. In the central nervous system, it fosters neuroinflammation that accelerates cognitive decline and neurodegenerative disorders(4). Within the cardiovascular system, it promotes endothelial dysfunction and atherosclerosis(5). In the respiratory tract, it contributes to chronic obstructive pulmonary disease and pulmonary fibrosis(6, 7). In musculoskeletal tissues, it drives sarcopenia and osteoporosis(8). These widespread impacts underscore inflammaging as a unifying mechanism that links aging with the onset and progression of age-related diseases. Understanding the cellular and molecular drivers of inflammaging is crucial for developing targeted interventions aimed at promoting healthy aging and delaying the onset of chronic diseases.

Targeting inflammaging has therefore emerged as a promising strategy for extending healthspan. Senolytics selectively eliminate senescent cells, while senomorphics suppress SASP production without inducing cell death(9). Modulation of gut microbiota through diet, probiotics, or prebiotics offers additional opportunities to attenuate systemic inflammation(10). Lifestyle interventions such as caloric restriction, exercise, and improved sleep quality further mitigate inflammatory burden(11). Together, these approaches highlight the therapeutic potential of addressing inflammaging at both molecular and systemic levels. This review aims to synthesize current knowledge on the molecular and cellular drivers of inflammaging, with particular emphasis on the mechanisms that sustain chronic inflammation in aging. Furthermore, it explores emerging interventions designed to counteract inflammaging and evaluates their potential to delay or prevent age-related diseases. By integrating mechanistic insights with therapeutic perspectives, this review seeks to provide a comprehensive framework for understanding inflammaging and to guide future strategies for promoting healthy aging.

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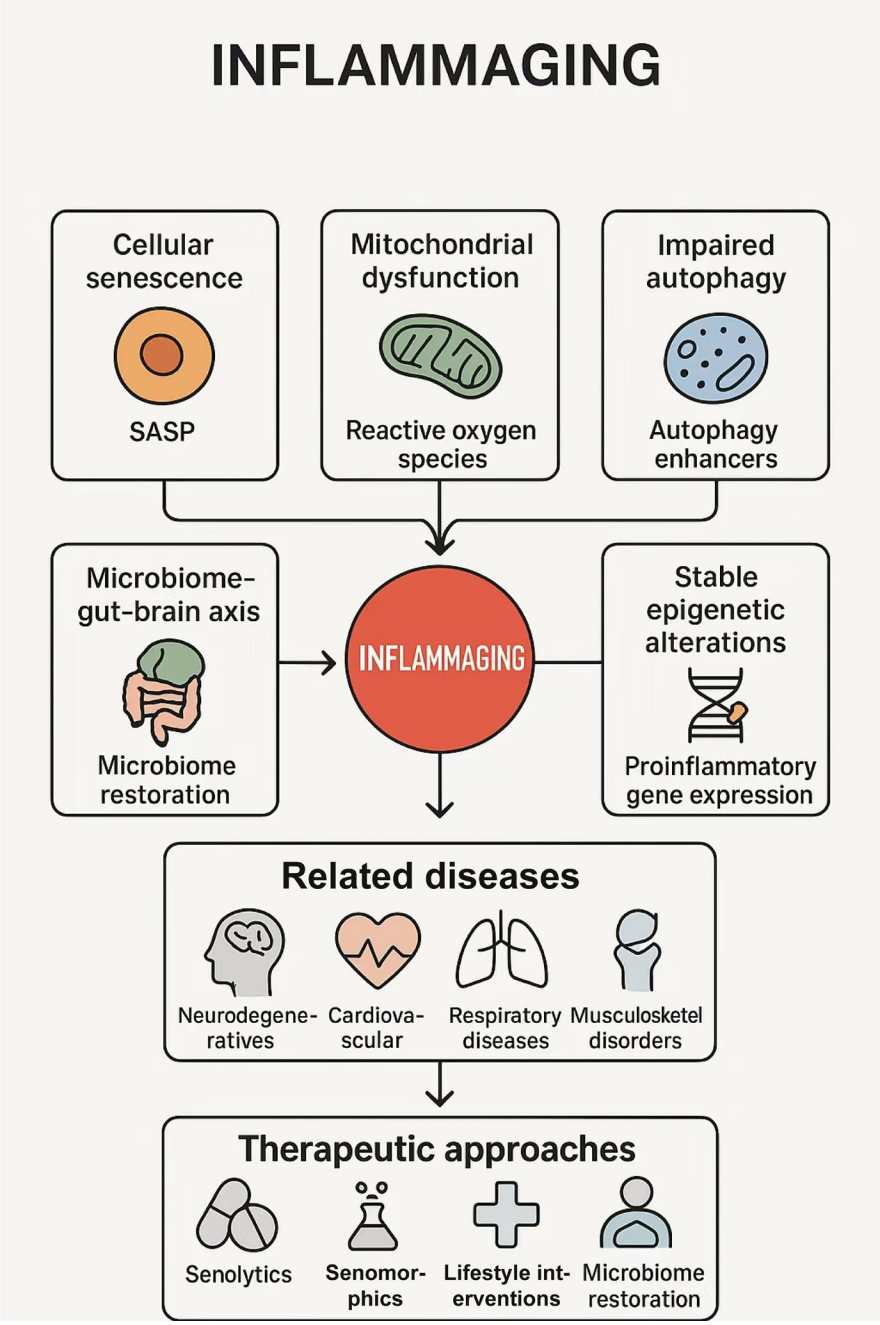

FIGURE 1

Mechanisms and therapeutic prospects of inflammaging.

Inflammaging results from the combined effects of multiple interconnected biological processes, including cellular senescence with secretion of the SASP, mitochondrial dysfunction with excessive production of ROS, impaired autophagy, dysregulation of the microbiome-gut-brain axis, and stable epigenetic changes that maintain pro-inflammatory gene expression. Treatments targeting these drivers primarily include the use of anti-aging drugs to eliminate senescent cells, SASP modulators to inhibit pro-inflammatory signaling, as well as microbiome modulation and lifestyle interventions. SASP: Senescence-associated secretory phenotype; ROS: Reactive oxygen species.

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The core driving mechanism of Inflammaging

Inflammaging differs fundamentally from acute inflammation, as it lacks resolution and is sustained by a continuous interplay between molecular damage, cellular senescence, innate immune activation, and metabolic dysregulation. Its progression is tightly associated with the accumulation of damage-associated molecular patterns (DAMPs), mitochondrial dysfunction, and defective autophagy(12). Senescent cells, which progressively accumulate with age, secrete a complex pro-inflammatory secretome termed the senescence-associated secretory phenotype (SASP), composed of cytokines, chemokines, growth factors, and proteases. This secretome not only reinforces senescence in neighboring cells but also fuels a chronic inflammatory milieu(13). Concurrently, dysregulation of innate immune sensing pathways—such as NF-κB, cGAS-STING, and NLRP3 inflammasome signaling—further amplifies inflammatory responses in the absence of pathogen-derived signals(14, 15). Mitochondrial DNA leakage, impaired mitophagy, and increased reactive oxygen species (ROS) production also contribute to a pro-inflammatory cellular environment(16). Moreover, alterations in the gut microbiota composition and increased intestinal permeability with age facilitate the translocation of microbial products into systemic circulation, enhancing immune activation and systemic inflammation. Epigenetic drift, metabolic reprogramming, and reduced anti-inflammatory regulatory mechanisms exacerbate this process, leading to sustained inflammatory signaling(17). Targeting key nodes within these pathways holds promise for delaying or reversing age-related inflammatory phenotypes and associated pathologies.

The central role of cellular senescence

Cellular senescence is a fundamental biological process defined by a stable cell cycle arrest triggered by diverse stressors, including telomere attrition, DNA damage, oxidative stress, or oncogene activation. Transient senescence exerts beneficial effects in tissue repair and tumor suppression; however, the long-term accumulation of senescent cells with age emerges as a major driver of inflammaging. These cells evade immune clearance and release a distinct set of bioactive molecules collectively termed the SASP. The SASP consists of a heterogeneous mixture of pro-inflammatory cytokines (e.g. IL-6, IL-1β, TNF-α), chemokines (e.g. CXCL8, CCL2), growth factors (e.g. VEGF, HGF), and matrix-remodeling enzymes (e.g. MMPs)(18). Together, these mediators sustain chronic tissue inflammation, thereby accelerating aging and fostering the onset of multiple age-related disorders. Circulating levels of SASP proteins such as GDF15, IGFBP2, and Cystatin-C have been shown to correlate with inflammatory markers including CRP and TNF-α, as well as with reduced muscle strength, serving as predictors of functional decline(19). Activation of NF-κB and C/EBPβ signaling plays a central role in SASP induction, while persistent DNA damage response (DDR) signaling acts as a critical upstream regulator of SASP gene expression(20).

Senescent cells exhibit resistance to apoptosis and progressively accumulate in tissues such as skin, adipose tissue, liver, and vascular endothelium. Their persistence has been directly associated with age-related pathologies. For example, increased senescent burden in adipose tissue correlates with insulin resistance and systemic inflammation in aged mice(21). In the context of COVID-19, SARS-CoV-2 infection has been reported to trigger cellular senescence and SASP release, thereby aggravating systemic inflammation(22). Declining immune surveillance further exacerbates this problem. With age, natural killer cells and macrophages lose efficiency in recognizing and clearing senescent cells, resulting in the persistence of these pro-inflammatory populations. The failure of immune-mediated clearance creates a self-reinforcing loop that perpetuates SASP-driven inflammation and accelerates tissue degeneration(23). Collectively, cellular senescence represents a pivotal mechanism linking cellular stress to systemic inflammation.

Mitochondrial dysfunction

Mitochondrial dysfunction is a central hallmark of aging and plays a pivotal role in the onset and maintenance of inflammaging. In senescent cells, mitochondria undergo profound structural and functional alterations, including increased mitochondrial mass, membrane depolarization,

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impaired oxidative phosphorylation, and elevated production of ROS. These changes disrupt cellular homeostasis and contribute to both the establishment of the SASP and the persistence of low-grade systemic inflammation. Elevated mitochondrial ROS production serves as a major trigger for DNA damage, which reinforces the DDR and sustains the secretion of SASP factors such as IL-6, IL-8, and MCP-1(24). ROS-mediated activation of redox-sensitive transcription factors, particularly NF-κB and AP-1, further amplifies the expression of inflammatory mediators. Mitochondrial DNA (mtDNA), when released into the cytosol due to membrane permeability defects, acts as a DAMP that activates innate immune pathways including the cyclic GMP-AMP synthase–stimulator of interferon genes (cGAS–STING) axis, triggering type I interferon responses and sustaining chronic inflammation(25). Moreover, defective mitophagy in aged cells impairs the clearance of damaged mitochondria, promoting their accumulation and exacerbating inflammatory signaling.

Mitochondrial dysfunction plays a key role in diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis. Mitochondrial DAMPs activate microglia, enhance neuroinflammation, and lead to neuronal damage and neurodegeneration. For example, in AD, mitochondrial dysfunction induces neuroinflammation and accelerates amyloid deposition and tauopathy(26). Furthermore, mitochondrial dysfunction is implicated in auditory system inflammation and may contribute to hearing loss through ion channel dysregulation(27). Mitochondrial dysfunction also damages vascular endothelial cells by increasing ROS and oxidative stress, promoting atherosclerosis and heart failure(28). Mitochondrial-related processes, such as metabolic abnormalities and dysregulated calcium homeostasis, contribute to chronic inflammation in the aging heart, which is considered a shared pathway in the pathogenesis of cardiovascular disease. For example, decreased mitochondrial function in the aging heart releases mtDNA, activating inflammatory responses and exacerbating cardiac fibrosis and dysfunction(29). Impaired immune surveillance further exacerbates the persistence of dysfunctional mitochondria within senescent cells. Aging-associated decline in autophagy, lysosomal capacity, and immune effector function allows these damaged organelles to persist, sustaining a chronic inflammatory state.

Impaired autophagy

The decline of autophagy with aging compromises cellular quality control, allowing damaged organelles, protein aggregates, and advanced glycation end products (AGEs) to accumulate(30). This defect fosters ROS production, activates inflammasomes, and drives persistent IL-1β release. Inefficient clearance of damaged mitochondria directly links impaired autophagy to mitochondrial dysfunction, thereby amplifying SASP-driven inflammation. In parallel, defective autophagy hinders the removal of misfolded proteins such as β-amyloid and α-synuclein, promoting their aggregation. Coupled with microglial activation during inflammaging, this process triggers chronic neuroinflammation and accelerates the progression of AD and PD(31). In PD models, impaired microglial autophagy exacerbates inflammatory signaling and promotes neuronal loss(32). Mitochondrial dysfunction further contributes by releasing ROS that intensify inflammatory stress.

Autophagy decline also disrupts immune surveillance by impairing the function of macrophages, dendritic cells, and natural killer cells. Reduced autophagic flux diminishes antigen processing efficiency, compromises pathogen clearance, and limits the removal of senescent cells, enabling pro-inflammatory cell populations to persist within tissues. In liver fibrosis, downregulation of autophagy-related genes such as RB1CC1 decreases macrophage infiltration, reflected by reduced F4/80 expression, and promotes hepatic stellate cell activation, thereby driving fibrotic progression(33). Converging lines of evidence support a causal relationship between autophagy deficiency and inflammaging. Restoration of autophagy through caloric restriction, mTOR inhibition, or pharmacological activators such as spermidine attenuates systemic inflammation and improves tissue integrity in aged animal models(34).

Dysbiosis of the microbiota-gut-brain axis (MGB)

MGB axis represents a bidirectional communication network linking the intestinal microbiota, gastrointestinal tract, and central nervous system through neural, endocrine, metabolic, and immune pathways(35). On the one hand, gut microbiome dysbiosis can trigger chronic systemic inflammation, disrupt the blood-brain barrier, lead to neuroinflammation and

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oxidative stress, and thus accelerate brain aging. On the other hand, stress or damage to the brain (e.g. through neuroendocrine signaling) can feedback and affect gut microbial composition and gut barrier function. This cycle is amplified during aging, creating a state of "inflammaging." Age-related changes in gut microbiome composition (termed dysbiosis) have profound effects on this axis, triggering systemic inflammation and contributing to the pathogenesis of inflammaging. Previous studies have shown that gut microbiome dysbiosis is a common feature of neurodegenerative diseases. Through the enrichment of pro-inflammatory microbes and the depletion of beneficial bacteria, it drives chronic inflammation and oxidative stress, ultimately leading to neuronal loss(36). This may represent a novel therapeutic target, such as modulating the microbiome to alleviate neuroinflammation.

Circulating microbial components act as potent pathogen-associated molecular patterns (PAMPs), activating Toll-like receptor (TLR) signaling in innate immune cells and triggering sustained production of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α(37). Chronic activation of these pathways reinforces low-grade systemic inflammation and disrupts tissue homeostasis. Furthermore, dysbiosis alters microbial metabolite profiles, including short-chain fatty acids (SCFAs) and tryptophan derivatives, which play crucial roles in regulating immune tolerance and maintaining the integrity of the blood–brain barrier (BBB). Reduced SCFA production impairs regulatory T cell (Treg) function, while increased levels of harmful metabolites exacerbate microglial activation within the central nervous system(38). Following traumatic brain injury, gut microbial dysbiosis promotes chronic overactivation of microglia(39). Depletion of the gut microbiome suppresses microglial activation, while restoration of the microbiome through fecal microbiota transplantation (FMT) reactivates microglia. In an ischemic stroke model, gut dysbiosis leads to microglial hyperactivation through SCFA and inflammatory cytokine signaling, and experimental interventions (such as specific oils) can reverse the dysbiosis and modulate microglial phenotype(40). Collectively, dysbiosis of the MGB axis acts as a persistent driver of chronic inflammation by compromising barrier integrity, altering immune signaling, and disrupting neuroimmune regulation.

Alterations in epigenetic regulation

Epigenetic regulation controls gene expression without altering DNA sequence, primarily through DNA methylation, histone modifications, and noncoding RNA networks. During aging, alterations in these regulatory pathways profoundly influence the transcriptional landscape of immune and stromal cells, leading to inflammaging(41). These changes result from cumulative environmental exposures, metabolic shifts, and persistent activation of stress response pathways. Global DNA hypomethylation is a hallmark of senescent cells, leading to genomic instability and derepression of transposable elements(42). Aberrations in DNA methylation patterns during aging contribute to disrupted biological processes and contribute to a variety of diseases, including cancer, neurodegenerative diseases, cardiovascular disease, and diabetes. This methylation dysregulation is directly involved in inflammaging-related events. Furthermore, site-specific hypermethylation occurs at the promoters of genes involved in anti-inflammatory signaling, suppressing the expression of immune regulatory factors. For example, hypermethylation of the IL-10 promoter in elderly individuals is associated with reduced IL-10 secretion, which is associated with increased systemic inflammation and an elevated risk of cardiovascular disease(43). In rheumatoid arthritis, similar hypermethylation patterns at immune regulatory sites exacerbate joint inflammation and disease severity(44).

Histone modifications and noncoding RNAs influence macrophage polarization, NLRP3 inflammasome activation, and other processes by regulating the expression of inflammation-related genes(45). Age-related increases in histone H3 lysine 9 trimethylation (H3K9me3) at specific sites lead to gene silencing essential for cellular stress adaptation, while decreases in acetylation marks (such as H3K27ac) impair chromatin accessibility of anti-inflammatory genes(46). These altered chromatin states promote sustained activation of proinflammatory transcription factors, including NF-κB and STAT3, thereby maintaining the SASP. The brains of patients with AD exhibit increased histone deacetylase (HDAC) activity, which represses the expression of neuroprotective genes and accelerates neuroinflammation, linking chromatin remodeling to neurodegeneration(47). Noncoding RNAs, particularly miRNAs and lncRNAs, are additional epigenetic regulators of inflammatory networks

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during aging. For example, overexpressed miR-21 and decreased miR-146a disrupt Toll-like receptor and cytokine signaling, thereby maintaining low-grade inflammation(48). In atherosclerosis, aberrant miRNA expression profiles promote macrophage activation and plaque instability(49). Similarly, lncRNAs such as NEAT1 are upregulated in type 2 diabetes, driving NLRP3 inflammasome activation and metabolic inflammation. Similarly, age-related changes in lncRNA expression are associated with enhanced inflammasome activity and impaired immune responses(50). These epigenetic alterations are not merely passive consequences of aging but rather active participants in the establishment of a proinflammatory state. Persistent epigenetic reprogramming locks immune and parenchymal cells into a maladaptive activation state, impairing their ability to restore homeostasis.

Therapeutic strategies targeting inflammaging

Given the central role of inflammaging in driving functional decline and age-related diseases, therapeutic strategies have increasingly focused on interventions that attenuate chronic inflammation while restoring tissue homeostasis. Among these approaches, the clearance of senescent cells has emerged as a pivotal avenue. Senolytic agents selectively induce apoptosis in senescent cells by disrupting their survival pathways, thereby reducing the accumulation of cells that perpetuate inflammatory signaling. Suppression of the SASP represents a complementary strategy. Senomorphic compounds act by dampening the secretion of pro-inflammatory cytokines, chemokines, and proteases without inducing cell death, thereby limiting tissue damage while preserving beneficial aspects of senescence such as tumor suppression(51). Targeting key regulators of SASP, including NF-κB, mTOR, and p38 MAPK, has shown promise in mitigating inflammaging across various models. Another therapeutic dimension involves modulation of the gut microbiota, a crucial determinant of systemic inflammation during aging. Restoration of microbial diversity through probiotics, prebiotics, or fecal microbiota transplantation reduces intestinal permeability, prevents translocation of microbial products, and attenuates chronic immune activation. Such interventions not only modulate inflammatory tone but also influence metabolic and immune functions critical for healthy aging(52). Lifestyle modifications provide an additional, non-pharmacological strategy to counter inflammaging. Caloric restriction, intermittent fasting, regular physical exercise, and improved sleep quality have each been shown to reduce systemic inflammatory burden, enhance mitochondrial function, and promote resilience against age-related decline(53). Collectively, these strategies underscore the multifaceted nature of combating inflammaging. By integrating cellular clearance, secretory modulation, microbiota regulation, and lifestyle adaptation, therapeutic interventions hold significant promise for extending healthspan and delaying the onset of chronic age-associated disorders.

Clearance of senescent cells

The targeted elimination of senescent cells has emerged as a pivotal therapeutic strategy to counteract inflammaging. Senescent cells, characterized by irreversible cell-cycle arrest and a persistent SASP, accumulate progressively with age in multiple tissues. Their prolonged survival, despite functional decline, contributes to chronic low-grade inflammation through sustained secretion of pro-inflammatory cytokines, chemokines, growth factors, and matrix-degrading enzymes. Removing these cells interrupts a central source of inflammatory mediators, thereby mitigating systemic inflammatory burden and restoring tissue homeostasis. Senolytic agents exploit the heightened dependency of senescent cells on anti-apoptotic pathways for survival. For example, ABT-263 and HSP90 inhibitors are being investigated for combating chronic inflammation in the cardiovascular system, thereby improving vascular function and structure(54, 55). In models of vascular health, these inhibitors have helped restore vascular health by reducing fibrosis and gene dysregulation. ABT-263 has been shown to reduce the risk of cardiovascular events in men (although the effect may be less pronounced in women). By eliminating cells with the SASP, ABT-263 inhibits inflammation, showing

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potential in cancer therapy. This strategy can reduce microenvironmental inflammation and may serve as an adjuvant therapy for cancers such as hepatocellular carcinoma. Combining it with ALK inhibitors such as lorlatinib can enhance the latter's anticancer efficacy, promote cancer cell apoptosis, and inhibit tumor growth(56). Furthermore, compounds such as dasatinib, a tyrosine kinase inhibitor, and quercetin, a plant-derived flavonoid, have demonstrated synergistic senolytic activity in kidney disease and skin cell aging by targeting BCL-2 family proteins and other survival networks(57).

Alternative approaches employ genetic strategies to selectively ablate senescent cells. The INK-ATTAC transgenic mouse model, which enables inducible elimination of p16^Ink4a-expressing cells, has provided compelling evidence that senescent cell clearance delays age-associated functional decline, improves physical performance, and extends median lifespan(58). Translational efforts are now exploring small-molecule senolytics, peptide-based agents, and nanocarrier-mediated drug delivery to improve specificity and minimize off-target effects. Early-phase clinical trials have reported that senolytic combinations can reduce markers of senescence and inflammation in humans, although long-term safety and efficacy remain under investigation. Removal of senescent cells not only reduces SASP-driven inflammatory signals but also creates a tissue environment more conducive to regeneration and immune surveillance, providing more effective treatment options for inflammatory aging-related diseases.

Inhibition of the SASP

Another therapeutic strategy targeting senescent cells is to use senomorphics, which aims to inhibit or delay phenotypes related to cellular senescence rather than directly eliminate senescent cells. The SASP constitutes a complex network of pro-inflammatory cytokines, chemokines, proteases, and growth factors secreted by senescent cells. While SASP plays beneficial roles in acute tissue repair and tumor suppression, its persistent activation during aging amplifies inflammaging and promotes the progression of age-related diseases(59). Targeting SASP directly has emerged as a viable therapeutic strategy, particularly when the preservation of transient, beneficial senescence is desirable.

Multiple intracellular pathways converge to regulate SASP expression. NF-κB functions as a central transcriptional driver, sustaining the production of IL-6, IL-8, and other inflammatory mediators. Pharmacological NF-κB inhibitors, including BMS-345541 and natural compounds such as parthenolide, have been shown to attenuate SASP output in preclinical models, thereby reducing local inflammation and preserving tissue integrity(60). The JAK/STAT pathway represents another critical axis, with JAK1/2 inhibition by ruxolitinib demonstrating efficacy in suppressing SASP-associated cytokine release, improving hematopoietic function, and treats immune-induced aplastic anemia(61). mTOR signaling, particularly through the mTORC1 complex, modulates SASP via translational control of IL-1α and other upstream regulators; rapamycin and its analogs, rapalogs, have successfully reduced SASP intensity and improved vascular and cognitive function in animal models(62).

Unlike anti-senolytic drugs, which aim to completely eliminate senescent cells, SASP inhibition focuses on reprogramming the secretory properties of senescent cells. This distinction is crucial in conditions such as wound healing, where senescent cells can provide transient benefits but their excessive inflammatory output is detrimental. However, SASP inhibition and senescent cell clearance agents can complement each other: senescent cell clearance agents can reduce the total number of senescent cells, while SASP inhibition can mitigate the inflammatory effects of remaining cells(63). Future therapeutic frameworks may combine SASP inhibition with senescent cell clearance strategies, microbiome modulation, and autophagy enhancement to more comprehensively control chronic inflammation in aging.

Regulation of intestinal flora

The gut microbiota plays a pivotal role in maintaining metabolic balance, immune homeostasis, and mucosal barrier integrity. Aging is often accompanied by dysbiosis, characterized by a reduction in beneficial commensals, expansion of opportunistic pathogens, and diminished microbial diversity. These changes compromise epithelial tight junctions, increase intestinal permeability, and facilitate translocation of microbial products such as lipopolysaccharides into the circulation, thereby fueling systemic inflammation(64). Interventions targeting the gut microbiota have therefore emerged as promising strategies

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to attenuate inflammaging. Probiotic supplementation replenishes beneficial bacterial populations and restores microbial balance. Strains such as Lactobacillus rhamnosus GG and Bifidobacterium longum have demonstrated the capacity to reinforce barrier function, enhance mucosal immune tolerance, and reduce pro-inflammatory cytokine production in colitis models(65). Prebiotics, including inulin and fructooligosaccharides, selectively promote the growth of these beneficial microbes, indirectly modulating the inflammatory tone of the host.

Preclinical studies have shown that FMT has attracted considerable attention due to its ability to reshape the entire microbial ecosystem. FMT from young donors significantly improved intestinal barrier integrity in aged mice, upregulated tight junction protein expression, and reversed the abnormal increase in aging-related inflammatory factors. This intervention also restored intestinal immune homeostasis and alleviated systemic inflammation (e.g. reduced serum levels of proinflammatory factors)(66). FMT can also reduce systemic inflammatory burden by modulating intestinal microbiota structure (e.g. increasing the abundance of beneficial bacteria) and SCFAs, inhibiting proinflammatory pathways such as NF-κB(67). In a vascular aging model, FMT from young donors delayed arterial endothelial dysfunction and vascular stiffness, while also alleviating insulin resistance and abnormal fat accumulation(66). The mechanism involves metabolic pathways regulated by the microbiota (e.g. bile acid metabolism). Early clinical data suggest potential benefits for metabolic and neurodegenerative diseases associated with intestinal microbiota dysbiosis. In terms of neuroprotection and improvement of cognitive function, FMT can repair the function of the "gut-brain axis", reduce neuroinflammation in the hippocampus of aged mice (such as inhibiting microglial activation and NLRP3 inflammasome expression), alleviate oxidative stress damage, and restore the balance of neurotransmitters in brain tissue(68). By restoring microbial diversity, enhancing barrier integrity, and reducing the systemic influx of pro-inflammatory signals, gut microbiota modulation addresses a fundamental upstream driver of inflammaging.

Lifestyle interventions

Lifestyle modifications represent a cornerstone in the non-pharmacological management of inflammaging, offering multifaceted benefits through metabolic, immunological, and epigenetic regulation. Unlike targeted molecular therapies, these approaches influence multiple upstream pathways, thereby producing systemic and sustained effects on inflammation and aging trajectories. Dietary interventions have shown profound effects on inflammatory tone and metabolic resilience. Caloric restriction without malnutrition consistently reduces circulating pro-inflammatory cytokines, improves mitochondrial efficiency, and enhances autophagic flux in both animal models and humans(69). The Mediterranean diet, rich in monounsaturated fats, polyphenols, and dietary fiber, promotes a microbiota composition associated with reduced intestinal permeability and lower systemic endotoxemia(70). Similarly, intermittent fasting regimens improve insulin sensitivity and modulate mTOR and AMPK signaling, attenuating age-related inflammatory activation(71).

Physical activity exerts anti-inflammatory effects through several mechanisms, including increased production of myokines with immunoregulatory properties, improved endothelial function, and reduction of visceral adiposity—a major source of inflammatory mediators(72). Regular aerobic and resistance training in older adults has been associated with lower C-reactive protein levels, preserved muscle mass, and enhanced immune surveillance. Importantly, exercise can synergize with dietary interventions to amplify anti-inflammatory effects. Sleep quality and circadian rhythm stability also influence inflammaging. Chronic sleep disruption elevates IL-6 and TNF-α, impairs immune cell trafficking, and accelerates epigenetic aging(73). Psychological stress management is another critical dimension. Persistent activation of the hypothalamic-pituitary-adrenal axis elevates glucocorticoid levels, disrupts immune homeostasis, and fosters chronic inflammation(74). Mind-body practices such as meditation, yoga, and controlled breathing have demonstrated measurable reductions in inflammatory biomarkers and improvements in autonomic balance(75). Integrating lifestyle interventions into clinical practice is equally important for improving patient outcomes. A comprehensive approach combining an optimized diet, structured exercise, adequate sleep, and stress reduction can provide a comprehensive approach to alleviating inflammaging. Future therapeutic frameworks may combine gut microbiota modulation with lifestyle modifications, such as dietary interventions, to achieve lasting improvements in host-microbiota symbiosis

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and systemic inflammatory status.

Conclusion

Inflammaging results from the combined effects of multiple factors, including cellular senescence, mitochondrial dysfunction, impaired autophagy, microbiome dysbiosis, and epigenetic alterations, creating a persistent cycle of low-grade sterile inflammation. These mechanisms gradually undermine tissue integrity, accelerate functional decline, and increase the susceptibility to chronic disease. Recent advances have highlighted the potential of multimodal interventions—combining senolytics, SASP modulators, immune reprogramming, autophagy enhancers, and microbiome restoration—to disrupt the inflammatory feedback loop and restore homeostasis. Lifestyle-based strategies, including caloric restriction and targeted dietary modifications, further complement drug treatment options. However, translating preclinical research findings into safe and durable human therapies remains challenging. Advancing these efforts is crucial for translating the concept of inflammaging into actionable strategies that can aid in the therapeutic intervention of inflammaging-related diseases and extend human healthspan.

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