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Review

Mitochondrial Inflammation and Muscle Aging: Targeting the Inflammatory Microenvironment in Sarcopenic Muscle

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ABSTRACT: Sarcopenia is an age-related progressive degenerative disorder of skeletal muscle characterized by declining muscle mass, strength, and function. Increasing evidence indicates that chronic low-grade inflammation plays an important contributory role in its pathogenesis. The inflammatory microenvironment contributes to sarcopenia through complex interactions involving cellular senescence, mitochondrial dysfunction, and sustained inflammatory signaling, forming a self-reinforcing pathological cycle within skeletal muscle. This review synthesizes current evidence on the molecular mechanisms underlying inflammation-driven sarcopenia, with particular emphasis on how inflammatory signaling disrupts protein turnover and satellite cell metabolism. In addition, exercise is examined as a precision "hormone-like" intervention tailored to different sarcopenia phenotypes, highlighting the distinct mechanisms through which resistance training, aerobic exercise, and combined training modulate the senescence-associated phenotype and inflammatory responses. The review further evaluates anti-inflammatory therapeutic strategies, including nutritional interventions, pharmacotherapy, and acupuncture. These approaches improve muscle health by restoring immune balance, enhancing mitochondrial function, modulating the gut-muscle axis, reducing oxidative stress, and promoting the clearance of senescent cells. Finally, emerging precision medicine frameworks and multi-omics strategies that may support individualized sarcopenia management are discussed. Overall, this review provides an integrated perspective on inflammatory signaling in sarcopenia and outlines potential therapeutic strategies targeting the inflammatory microenvironment, offering insights for future research and clinical management.

Keywords: sarcopenia, muscle, aging, inflammaging, DAMPs, therapy

1. Introduction

Sarcopenia is a progressive, age-related skeletal muscle disorder that is associated with increased risks of reduced mobility, complications, and mortality [1]. The European Working Group on Sarcopenia in the Elderly defined sarcopenia as a decline in both muscle mass and function [2]. Its complex pathogenesis involves molecular, cellular, and systemic imbalances, referred to as inflammaging, which is a chronic low-grade inflammation that contributes to muscle atrophy [3, 4]. This inflammatory state disrupts protein turnover, impairs mitochondrial function, and accelerates cellular senescence, thereby creating a cycle of progressive muscle decline [5].

Mitochondria are important regulators of inflammatory signaling beyond energy metabolism [6]. Under stress, they release damage-associated molecular

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patterns (DAMPs), including mtDNA, succinate, cardiolipin, N-formylpeptides, and ATP, which activate pattern recognition receptors in immune and muscle cells [7]. This phenomenon triggers proinflammatory cytokine cascades and increases oxidative stress via mitochondrial reactive oxygen species [8], accelerating protein degradation and suppressing synthesis to cause net muscle loss. Further, senescence intensifies the aged muscle microenvironment [9]. Accumulated senescent cells secrete the senescence-associated secretory phenotype (SASP), which is a mix of proinflammatory cytokines, chemokines, and growth factors [10]. SASP sustains local inflammation, induces senescence in neighboring cells, and impairs muscle satellite cell regeneration [11]. Consequently, sarcopenia therapies must target this inflammatory cascade and its drivers.

Some promising interventions include exercise, nutrition, pharmacotherapy, and integrated approaches. Physical activity exerts anti-inflammatory effects by regulating immune lineages, enhancing mitochondrial quality control, and reducing SASP factors [12]. Nutritional strategies suppress inflammation and support muscle metabolism via the gut–muscle axis [13]. The pharmacological options include drugs targeting inflammatory pathways and emerging senolytic agents [14]. Moreover, complementary therapies, including acupuncture, electroacupuncture and MSCs-based treatment, exert broad protective effects by improving mitochondrial function, promoting macrophage polarization toward the reparative M2 phenotype, and restoring neuroendocrine-immune homeostasis in aged muscle tissue [15, 16].

This review aimed to assess current evidence on the interplay between inflammaging, mitochondrial dysfunction, and cellular senescence in driving sarcopenia. It also examined how DAMPs initiate and sustain muscle inflammation, analyzed the impact of inflammatory signaling on metabolism and regeneration, and evaluated therapeutic strategies, from exercise and nutrition to pharmaceuticals and complementary medicine. By validating these mechanisms, we identified novel targets and integrated approaches to preserve muscle health and function in elderly individuals.

2. Chronic Inflammation and Mitochondrial Dysfunction in Muscle Atrophy

2.1 Inflammation Induced by Mitochondrial Release of DAMPs

Mitochondria maintain energy metabolism and redox balance while regulating inflammation via the release of DAMPs. Under stress or injury, they release DAMPs, such as succinate, cardiolipin, N-formyl peptides, mtDNA, and ATP, which trigger immune responses by engaging specific pattern recognition receptors [7].

Succinate, a tricarboxylic acid cycle intermediate, promotes the differentiation of T helper 17 cells by stabilizing hypoxia-inducible factor-1, thereby increasing the secretion of interleukin (IL)-17 [17]. N-formyl peptides stimulate formyl peptide receptors on neutrophils and macrophages, driving chemotaxis, inflammatory mediator release, and the production of reactive oxygen species (ROS) [18]. mtDNA activates Toll-like receptor 9 to stimulate nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling and the release of proinflammatory cytokine [19, 20]. Further, mtDNA engages the cyclic GMP-AMP synthase-STING1 pathway to induce interferon beta-1, IL-6, and tumor necrosis factor-alpha (TNF-α) [21]. Extracellular ATP and mitochondrial cardiolipin activate and bind to the NLRP3 inflammasome, respectively, which increases the production of IL-1β and IL-18 [22-24]. In addition, mtROS enables NLRP3 binding to oxidized mtDNA, sustaining inflammation that contributes to muscle atrophy. Although NLRP3 deficiency extends health span and performance in mice, its abnormal activity causes chronic muscle wasting [25, 26]. Such dysregulation amplifies cytokines and suppresses peroxisome proliferator-activated receptor-gamma coactivator-1-alpha (PGC-1α), the central regulator of mitochondrial biogenesis, thereby destabilizing the ROS balance (Fig. 1) [27]. Finally, the release of muscle injury-induced DAMPs activates macrophages and recruits immune cells, which initiates a cytokine cascade that exacerbates tissue damage and triggers apoptosis-related dysfunction (Table 1) [28, 29].

DAMPs-induced chronic inflammation further disrupts mitochondrial quality control by inhibiting PINK1/Parkin-mediated mitophagy [30]. DAMPs trigger NF-κB activation and the subsequent secretion of TNF-α and IL-1β, which impairs the recruitment of Parkin to injured mitochondria and stalls mitophagic clearance [31]. This accumulation of damaged mitochondria, coupled with defective clearance, reduces cell viability. Consequently, these processes disrupt mitochondrial function via multiple regulatory pathways, driving a sustained pathological cycle of muscle deterioration.

2.2 Impact of Inflammatory Signals on Muscle Metabolism

2.2.1 Inflammatory Signaling and Muscle Protein Turnover

Skeletal muscle mass relies on a balance between protein synthesis and degradation, which is disrupted by inflammation through various pathways. In patients with

critical illness, muscle biopsies show elevated levels of apoptosis markers and increased caspase activity [32]. These indicators are associated with cellular stressors, including oxidative imbalance, mitochondrial proapoptotic signals, impaired PI3K-Akt signaling, and dysregulated cytokine production [33].

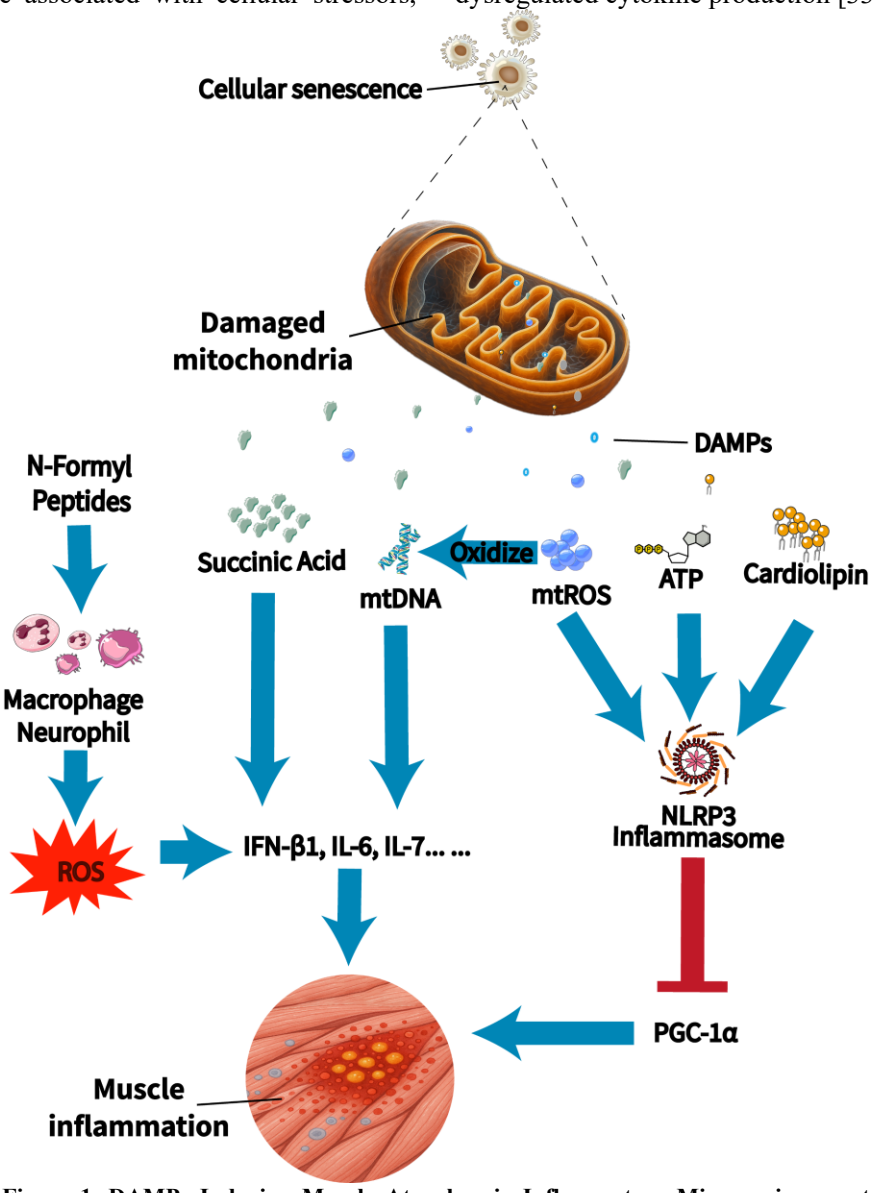

Figure 1. DAMPs Inducing Muscle Atrophy via Inflammatory Microenvironment Modulation. In senescent cells, mitochondrial dysfunction leads to the release of large amounts of DAMPs. These endogenous molecules induce inflammation in skeletal muscle cells, ultimately resulting in reduced muscle synthesis.

Inflammatory cytokines are important in muscle atrophy. IL-6 and TNF-α activate the JAK/STAT pathway, inducing E3 ubiquitin ligases and myostatin, which drive proteasome-mediated protein degradation [34, 35]. IL-6 further stimulates the expression of alpha-smooth muscle actin and the activiation of NLRP3, which increase inflammation [36]. In addition, high levels of IL-6 induce SOCS3 via JAK/STAT3 signaling [37]. Subsequently, SOCS3 inhibits insulin receptor substrate 1 (IRS-1), suppressing the insulin-like growth factor 1 (IGF-1)/Akt pathway and reducing protein synthesis [37]. Clinical data have shown that IL-6 alters systemic amino acid metabolism, which reduces plasma availability and decreases muscle protein turnover into half [5]. Myostatin also suppresses synthesis by regulating mTORC1 via AKT-mediated TSC2 phosphorylation while simultaneously promoting atrophy markers Atrogin-1 and MuRF1 via Smad2/3 and FoxO signaling [38]. Collectively, these cytokines disrupt homeostasis through multiple catabolic pathways [39].

Table 1. DAMPs Inducing Muscle Atrophy via Inflammatory Microenvironment Modulation.

DAMPs	Inflammatory Microenvironment Mediation	Mechanisms Impacting Muscle Atrophy
Succinate	Promotes Th17 cell differentiation; Induces IL-17 secretion [17]; Stabilizes HIF-1α	Induces mitochondrial ROS accumulation in tissues [223]
Cardiolipin	Activates NLRP3 inflammasome; Triggers oxidative stress	Disrupts ROS production/clearance balance; Reduces PGC-1α's anti-inflammatory and antioxidant functions [78]
N-formyl peptides	Activates FPRs; Induces inflammatory mediators and ROS [18]	Disrupts mitochondrial membrane potential, causes respiratory chain complex abnormalities, promotes cytochrome c release, and downregulates TFAM expression, disrupting mtDNA copy number [224]; directly inhibits protein synthesis, increases muscle protein susceptibility to proteolysis, synergizes with glucocorticoids to promote catabolism, activates the JAK/STAT pathway inducing E3 ubiquitin ligase and myostatin activation, and alters systemic amino acid metabolism [36]
mtDNA	Activates NF-κB signaling; Increases pro-inflammatory cytokines and type I interferons [19, 20]	Disrupts mitochondrial energy metabolism; Modulates respiratory chain complex assembly/activity; Impairs oxidative phosphorylation efficiency; Increases Drp1 activity [225]
ATP	Activates NLRP3 inflammasome; Increases IL-1β and IL-18 [22, 23]	Disrupts ROS production/clearance balance; Reduces the anti-inflammatory and antioxidant functions of PGC-1α [78]

DAMPs: damage-associated molecular patterns; Th17: T helper 17 cell; IL: interleukin; HIF-1α: hypoxia-inducible factor 1α; ROS: reactive oxygen species; NLRP3: NOD-like receptor family pyrin domain-containing 3; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1α; FPRs: formyl peptide receptors; TFAM: mitochondrial transcription factor A; mtDNA: mitochondrial DNA; NF-κB: nuclear factor κB; Drp1: dynamin-related protein 1; ATP: adenosine triphosphate.

Aging-related muscle atrophy differs from disease-related atrophy. As the condition involves the gradual loss of muscle mass, particularly type II fibers, it is driven by declining mitochondrial function and persistent cellular hypoxia [40]. These conditions increase the production of ROS and superoxide, which inhibit protein synthesis and renders myofibrillar proteins more susceptible to proteolysis via oxidative modification [40]. These findings confirmed the molecular mechanisms linking muscle atrophy to inflammatory signaling [3, 4].

2.2.2 Inflammatory Signaling and Cell Metabolism

Inflammatory signals regulate the regenerative capacity of muscle satellite cells by altering their energy metabolism. The interaction between satellite and immune cells forms a regulatory network during skeletal muscle repair. Satellite cells remain quiescent beneath the basal lamina of muscle fibers. After muscle injury, immune cells are recruited to the damaged site and they regulate satellite cell activity through cytokines and growth factors [41]. In particular, macrophages coordinate regeneration by interacting directly with myogenic precursor cells [42].

Macrophage polarization shifts dynamically during muscle repair. Initially, damaged tissues release IL-6 and TNF-α, which drives macrophages toward an M1 phenotype to promote myoblast and satellite cell proliferation [42]. As repair progresses, Meteorin signaling transitions macrophages to an anti-inflammatory (M2) state. Then, M2 macrophages release TGF-β, IL-10, IGF-1, and vascular endothelial growth factor to stimulate satellite cells and support myogenic differentiation into mature myofibers [43]. The additional mechanisms include macrophage subsets that promote satellite cell division via NAMPT-CCR5 signaling [44]. The glutamine uptake via SLC1A5 activates mTOR in satellite cells, coordinating proliferation and differentiation [45].

Other immune cells, including eosinophils and regulatory T cells, further support muscle regeneration. Eosinophils promote myogenesis by secreting IL-4 to act on fibro/adipogenic progenitors (FAPs) [46]. Tregs facilitate myoblast differentiation via relaxin and regulate macrophage phenotypes [47]. Notably, aged skeletal muscle exhibits blunted eosinophil recruitment and impaired Treg accumulation following injury, alongside reduced IL-10 secretion, thereby disrupting the coordinated immune signaling required for effective repair [46]. These interactions emphasize a complex regulatory network where macrophage transitions and satellite cell metabolic reprogramming can be key therapeutic targets for muscle regeneration disorders.

2.3 Cellular Senescence as a Hub for the Regulation of Inflammation

2.3.1 Inflammatory Microenvironment and Cellular Senescence

Cellular senescence, which is a state of permanent cell cycle arrest, balances tumorigenesis prevention with tissue homeostasis. In the skeletal muscle, senescence

drives functional decline via elevated production of ROS, mitochondrial dysfunction, and persistent inflammation [48]. Senescent cells release various inflammatory cytokines and growth factors, including IL-6, IL-8, IL-1β, TNF-α, TGF-β, and IGF-1. These secreted factors promote chronic local inflammation and propagate senescence to adjacent cells [49, 50]. Collectively, these molecules form the SASP, which drives the progression of sarcopenia [51]. In C2C12 myoblasts, the overexpression of endothelin-1 receptors accelerates senescence, which may interact with IGF-1 deficiency to exacerbate atrophy [52]. Ultimately, reduced IGF-1 production in disused or aged muscles significantly contributes to cell loss [53].

FAPs are skeletal muscle stromal cells that maintain homeostasis and facilitate repair [54]. By regulating fibrotic scarring and fat accumulation, they influence muscle resolution and atrophic progression [55]. FAPs preserve muscle structure by coordinating extracellular matrix remodeling and secreting paracrine factors that regulate satellite cell differentiation [55, 56]. With aging, FAPs adopt a proinflammatory phenotype, increasing the secretion of IL-33 and other cytokines/chemokines, which activates macrophages and increases the production of TNF-α and IL-6 [57]. Consequently, the levels of circulating TNF-α and IL-6 reflect FAP activity, indicating that age-related FAP dysregulation drives chronic inflammation underlying sarcopenia [58, 59].

Age-related declines in muscle regeneration stem from intrinsic mechanisms, such as cellular senescence, and extrinsic factors, such as SASP-mediated inhibition of proliferation. IGF-1 supports repair in young muscles, and its reduced expression in aged tissues worsens sarcopenia by impairing satellite cell proliferation and differentiation, compromising injury recovery [10, 60, 61]. S100A8/A9-positive immune cells, primarily activated neutrophils and macrophages, also accumulate in aged muscles. This phenomenon exacerbates inflammation and suppresses repair [9]. Transcriptomic and proteomic analyses confirm these distinct aging phenotypes, characterized by downregulated structural and metabolic genes, activated inflammatory pathways, and increased S100A8/A9-positive cell infiltration [62]. These shifts reflect dysregulated homeostasis, driving persistent low-grade inflammation and metabolic dysfunction.

Immune system aging further disrupts the skeletal muscle microenvironment. Senescent immune and nonimmune cells promote the development of SASP, indicating health decline, frailty, and age-related disease progression [52, 63, 64]. This phenomenon occurs via two mechanisms: impaired senescent cell clearance and persistent proinflammatory secretion. In particular, aging innate cells, such as macrophages, lose clearance capacity, allowing senescent cells to accumulate and secrete excessive cytokines and chemokines [65]. These processes amplify inflammation, and dysfunctional mitochondria exacerbate oxidative stress via the release of ROS and DAMPs. Taken together, these factors form a self-reinforcing cycle of muscle degeneration, positioning cellular senescence as an important link between inflammation and sarcopenia.

2.3.2 Mitochondrial Dysfunction Driven by Cellular Senescence

Skeletal muscle mitochondrial function progressively declines with aging. As a result, the efficiency of oxidative phosphorylation, the production of ATP, and the activity of electron transport chain complexes I and IV reduce [1, 66, 67]. The functional changes in electron transport chain complexes during aging show significant heterogeneity across tissues. For example, in the cardiac muscle, particularly within the interfibrillar mitochondria, aging is accompanied primarily by the decreased activities of complexes III and IV [68]. In contrast, in the skeletal muscle, liver, and brain, complex I is generally more sensitive to advancing age. For example, myoblasts rendered senescent via the overexpression of DNA methyltransferase 3a exhibit reduced complex I activity, increased ROS production, and disrupted membrane potential, which are factors that can trigger muscle inflammation [69]. Ultimately, these metabolic shifts impair contractility and drive aging via interconnected molecular mechanisms.

Partial mitochondrial outer membrane permeabilization in mitochondrial subsets characterizes cellular senescence. It promotes mtDNA leakage into the cytosol, which activates the SASP via the cGAS-STING pathway and links mitochondrial dysfunction to senescence [11]. Reduced respiratory capacity and decreased steady-state mitochondrial membrane potential (MMP), which defines the capacity for an efficient ATP production, are hallmarks of dysfunction in aged tissues [66]. The reduced respiratory capacity of mitochondria and decreased steady-state MMP are the decisive characteristics of mitochondrial dysfunction in aged tissues and senescent cells. During mitochondrial dysfunction in senescent cells, a low MMP is often associated with increased ROS production [70]. An increase in ROS production causes mtDNA mutations, induces protein and lipid oxidation, and increases oxidative stress, creating a self-reinforcing cycle that accelerates skeletal muscle aging [71].

Age-related mitophagy failure further promotes the accumulation of dysfunctional mitochondria, worsens energy deficits, and increases the production of ROS. PGC-1α is the master regulator of oxidative metabolism

and mitochondrial ROS production [72]. It promotes mitophagy by enhancing the lysosomal clearance of damaged mitochondria, reducing the accumulation of DAMPs, and limiting inflammation [73, 74]. In addition, it interacts with the p65 subunit of NF-κB, suppressing its transcriptional activity and blocking the expression of downstream proinflammatory genes [75]. Elderly patients with sarcopenia exhibit a prominent transcriptional signature of skeletal muscle mitochondrial bioenergetic dysfunction, characterized by a low PGC-1α/ERRα signaling [76]. As cells age, the decline in PGC-1α signaling results in the loss of ability to regulate inflammation, and the upregulation of adhesion molecules such as TNF-α, VCAM-1, and MCP-1 further induces skeletal muscle inflammation [77, 78].

DRP1 regulates mitochondrial fission, and MFN1 controls mitochondrial fusion. In senescent cells, mitochondrial dynamics shift toward excessive fission caused by an augmented DRP1 activity and reduced MFN1-mediated fusion [79]. This imbalance fragments the mitochondria, disrupts organelle function, and releases mitochondrial double-stranded RNA (mt-dsRNA) into the cytosol. Persistent accumulation of mt-dsRNA activates MAVS-dependent signaling, sustaining SASP-driven inflammation [80, 81]. These disturbances link mitochondrial dynamic imbalance to tissue degeneration and age-related pathologies (Fig. 2) [11].

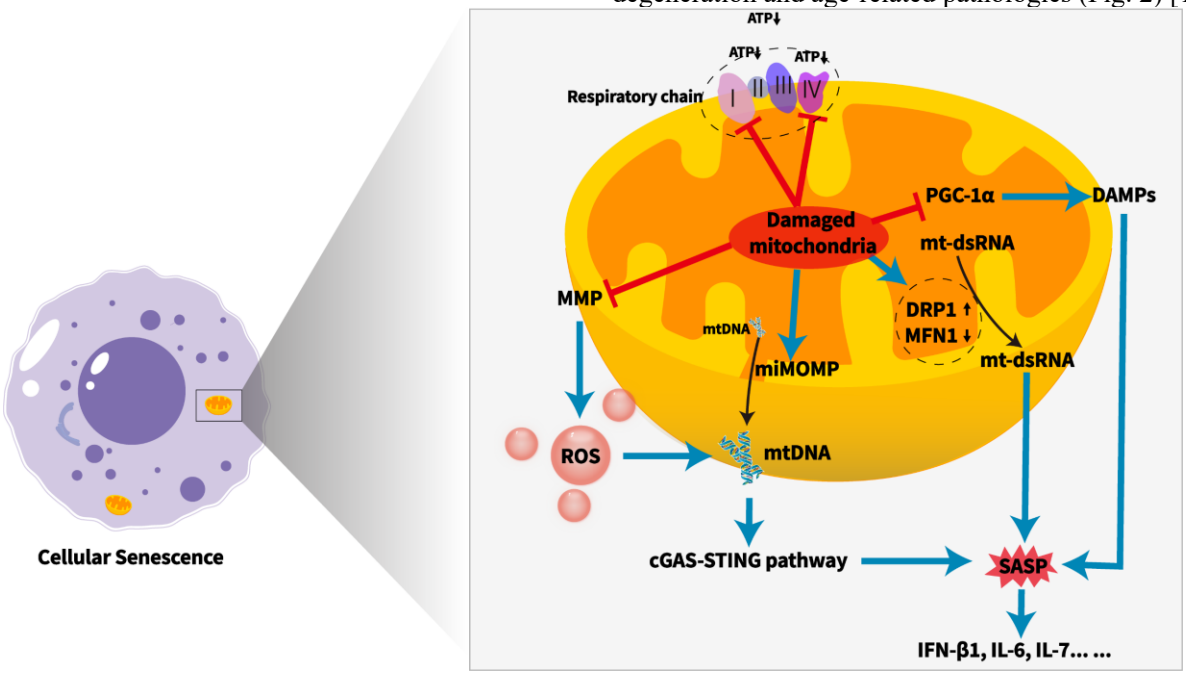

Figure 2. Cellular senescence induces mitochondrial inflammation. Aging leads to decreased efficiency of mitochondrial oxidative phosphorylation, reduced membrane potential, and excessive ROS production, which in turn induce mtDNA damage and protein oxidation. Concurrently, diminished mitophagy, imbalanced mitochondrial dynamics, and decreased PGC-1α signaling collectively promote the accumulation of dysfunctional mitochondria. These mitochondria activate the cGAS-STING pathway and SASP through the release of molecules such as mtDNA, ultimately driving chronic inflammation and muscle functional decline.

3. Multiple Anti-Inflammatory Therapies for Preserving Muscle Mass and Function

3.1 Exercise and Muscle Immune Regulation

3.1.1 Resistance Training

The impact of exercise on muscle inflammation depends on modality, intensity, frequency, and individual variability. Different modalities exert distinct effects on inflammatory markers and DAMPs in sarcopenia (Table 2).

Resistance training can suppress the development of inflammation in Sarcopenia. Experimental evidence shows that resistance training attenuates high-fat diet-induced activation of the NLRP3 inflammasome in adipose tissues [82]. Clinically, an 8-week resistance training stimulates autophagy, prevents NLRP3 inflammasome activation, and reduces apoptosis in peripheral blood mononuclear cells from older adults [83].

Cellular senescence markers, including $p16^{INK4a}$, $p21^{Cip1}$, and senescence-associated β-galactosidase (SA-β-Gal), exacerbate sarcopenia by inducing cell cycle arrest and a proinflammatory SASP that disrupts muscle

regeneration [84]. Physical exercise regulates this process at multiple levels. Experimental studies have shown that exercise reduces the expression of $p16^{INK4a}$, $p21^{Cip1}$, and SA-β-Gal in the muscle and tendon tissues of senescent rodents but not in young ones [85]. This selective clearance of senescent cells via exercise, without disturbing physiological aging, indicates clinical safety [86].

Table 2. The Impact of Different Training Methods on the Inflammatory Microenvironment in Sarcopenia Patients.

Author	Participant Group	Age	Exercise Mode	Training Program	Mechanism
Ke-Vin Chang et al. [226]	Control group: 44 females,13 males Case group: 44 females, 13 males	75.0 ± 5.9 years	RT	12 weeks, 12 sessions/week, 50 minutes/session	Reduced TNF-α, IL-1β, and IL-6 levels; decreased NF-κB activation; promoted muscle protein synthesis
Helton de Sá Souza et al. [227]	Control group: 14 participants RT group: 14 participants	Control group: 74.6 ± 7.13 years Resistance training group: 77.4 ± 6.25 years	RT (progressive)	12 weeks, 3 sessions/week (8 exercises, incremental load: 50%→75% 1RM)	Increased IL-10 secretion; elevated IL-1 receptor antagonist levels
Suk-Ling Ma et al. [140]	Control group: 6 females,6 males Exercise group: 6 females, 5 males Combination group (exercise + nutritional supplementation): 12 females, 11 males	Control group: 69.3 ± 3.8 years Exercise group: 76.4 ± 7.4 years Combined group: 73.7 ± 6.1 years	CT (RT + AE)	12 weeks, 1 session/week, 50 minutes/session (RT: 20-30 minutes + AE: 20 minutes)	Regulated IL-7R, PRKCQ expression; increased muscle protein synthesis
Seung-Jae Heo et al. [228]	39 females, 42 males	67.62 ± 4.48 years	RT (progressive)	12 weeks, 3 sessions/week, 50 minutes/session	Reduced TNF-α, IL-6; increased IL-10 secretion and muscle synthesis
Kuo-Jen Hsu et al. [229]	15 studies (≈500 participants; majority female)	68.1 ± 7.2 years	RT, AE, CT	RT: 12 weeks, 3 sessions/week (40-75% 1RM); AE: 8-24 weeks, 3 sessions/week (40-45 minutes/session); CT: 12 weeks, 3 sessions/week	RT: Increased muscle synthesis; AE: Reduced CRP and fat mass; CT: Reduced IL-6 and increased muscle function
Chun-Wei Li et al. [230]	Control group: 30 females, 26 males Case group: 18 females, 14 males	Control group: 65.24 ± 4.05 years Case group: 72.05 ± 6.54 years	RT	12 weeks, 3 sessions/week, 30 minutes/session (5-min warm-up + 20-min RT + 5-min slow walking)	Reduced TNF-α, TWEAK, IL-18; activated IGF-1 pathway; increased metabolic-inflammatory status
Mortaza Ghayomzadeh et al. [231]	Control group: 19 participants CT group: 18 participants	Control group: 37.9 ± 5.1 years Combined training group: 38.3 ± 4.9 years	CT (RT + AE)	6 months, 3 sessions/week, 70 minutes/session (resistance: periodized; aerobic: 20 minutes at 65-80% max heart rate)	Reduced TNF-α and IL-6; downregulated Myostatin; increased IGF-1 secretion
Shehab M Abd El-Kader et al. [101]	RT group: 30 participants; AE group: 30 participants	61-66 years	RT, AE	6 months, RT: 3 sessions/week, 40 minutes/session; AE: 3 sessions/week, 40 minutes/session	RT: No significant changes in inflammatory markers; AE: Reduced TNF-α, IL-6; increased IL-10 and T-cell counts
André Bonadias Gadelha et al. [232]	107 participants (gender unspecified)	65.4 ± 3.7 years	RT	24 weeks, 3 sessions/week, 40 minutes/session	Reduced TNF-α, IL-6; increased IL-10; increased iron metabolism and muscle synthesis
Andrea Tryfonos et al. [107]	COM group: 7 males HIIT group: 6 males	51 ± 13 years	HIIT	3 months	Reduced IL-8, TNF-1
Barbara Morawin et al. [233]	72 females, 8 males	70 ± 5.8 years	Low-intensity continuous training	10 months, 2 sessions/week, 40 minutes/session	Reduced Caspase 8/9 activity; inhibited apoptosis and inflammation

RT: Resistance training; AE: Aerobic exercise; CT: Combined training; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin; NF-κB: Nuclear factor kappa B; 1RM: One-repetition maximum; IGF-1: Insulin-like growth factor 1; CRP: C-reactive protein; HIIT: High-intensity interval training.

Human studies corroborate the abovementioned outcomes. Resistance training reduces the expression of p16INK4a in monocytes and vascular endothelial cells among middle-aged and elderly individuals [87]. Twelve weeks of combined strength and endurance training can downregulate the level of T-cell senescence markers and

circulating SASP factors [88]. In addition, resistance exercise triggers the mTOR pathway to enhance autophagic activity and facilitate targeted clearance of senescent cells [89, 90]. These findings may have important implications for the design of preventive and rehabilitative programs implemented in older populations.

3.1.2 Aerobic Training

Experimental findings have revealed that aerobic training exerts multilevel protective effects against inflammation [91]. Its direct anti-inflammatory capacity relies on regulating macrophage polarization. Excessive M1 macrophage activity in the sarcopenic muscle secretes proinflammatory cytokines and causes tissue damage. Exercise activates STAT3 signaling to promote macrophage transformation into the M2 phenotype and rebuild internal homeostasis [92-94]. M2 macrophages produce IGF-1 and IL-10 to form a beneficial microenvironment for satellite cell regeneration [12]. In addition, aerobic exercise modulates the SOCS1/STAT1/STAT3 pathway and activates PPARγ receptors. Further, it inhibits the P2X4/p38MAPK cascade and limits the secretion of IL-1β from M1 macrophages [94-96]. Such biological changes stabilize muscle protein metabolism and alleviate inflammatory degradation. Relevant experiments have validated that moderate exercise preconditioning restrains abnormal NLRP3 activation after acute exercise. Further, it offers practical references for the development of rational training [97].

Clinical findings support the abovementioned regulatory effects. Moderate jogging can inhibit NLRP3 inflammasome activity in the peripheral blood mononuclear cells of healthy young populations [98]. Training outcomes vary significantly with exercise intensity. Moderate-intensity inhibits abnormal NLRP3 overactivation. Excessively intense exercise may trigger an inflammasome response and weaken immune function [99, 100]. Resistance training contributes to muscle mass growth and strength improvement but exhibits inconsistent anti-inflammatory performance. Compared with resistance training, long-term aerobic training has better effects in reducing serum TNF-α and C-reactive protein (CRP) levels among elderly people [101, 102].

3.1.3 High-Intensity Interval Training

Exercise exerts bidirectional regulation on reactive ROS. ROS poses cytotoxic effects under resting conditions while serving as an essential signaling messenger during physical exercise [103]. It triggers antioxidant enzyme production via the Nrf2/ARE pathway and blocks the nuclear translocation of NF-κB [104]. High-intensity interval training (HIIT) boosts antioxidant defense and mitophagy activity. This intervention restrains the infiltration of proinflammatory macrophages and facilitates skeletal muscle repair in animal models of sarcopenia [105].

Clinical findings have confirmed that HIIT relieves inflammatory responses by reshaping muscle metabolic profiles and stabilizing intracellular energy metabolism [106]. Based on several analyses of skeletal muscle, sustained HIIT intervention upregulates the expression of genes associated with inflammation and tissue remodeling [107]. HIIT increases nuclear PGC-1α content in the human skeletal muscle. Subsequently, it regulates NLRP3 inflammasome function and drives mitochondrial biogenesis [99, 100, 108]. Resistance training can hardly raise PGC-1α levels to the same extent as HIIT [109]. Under identical total training volume, HIIT and moderate-intensity continuous exercise activate PGC-1α mRNA and its upstream signaling pathways at similar degrees [110].

Despite a similar activation of the PGC-1α pathway between the two exercise modes, relevant animal experiments have shown that HIIT provides stronger anti-inflammatory effects and superior skeletal muscle protection [105].

3.1.4 Combination Training

Combined training integrates multiple exercise modalities, producing additive anti-inflammatory and muscle-protective effects that are superior to single-mode training. Animal studies have shown that aerobic exercise reduces skeletal muscle oxidative stress, resistance exercise preserves antioxidant defenses, and combined training is more effective in attenuating oxidative damage and muscle catabolism [111].

Consistent with these mechanistic findings, clinical trials have validated the efficacy of combined exercise interventions for sarcopenia. Combined aerobic and resistance training downregulates the expression of skeletal muscle proinflammatory genes (TLR2, CD68), upregulates the production of anti-inflammatory TGF-β1, and improves muscle protein synthesis and myocellular quality [112]. A 6-month randomized controlled trial has shown that combined training significantly reduces the levels of circulating pro-inflammatory cytokines IL-6 and TNF-α and increases appendicular lean mass and physical function [113]. Notably, the increased load of combined training may exceed tolerance in older adults with sarcopenia, thereby resulting in the need for individualized risk assessment.

3.1.5 Differences and Associations of Inflammation in Exercise-Modified Sarcopenia

Sarcopenia can also be caused by other underlying conditions. In tumor-induced sarcopenia, tumor cells interact with surrounding cells to produce a mixture of catabolic and proinflammatory mediators [114]. These tumor-derived factors further stimulate the body to produce a cascade of inflammatory products. In addition, tumor cells secrete extracellular vesicles that migrate via the circulatory system, delivering their inflammatory cargo to multiple organs, including the muscle [115]. Recently, several newly identified molecules have been implicated as drivers of cancer-associated muscle wasting.

Leukemia inhibitory factor (LIF) was originally identified as a factor that inhibits the proliferation of murine myeloid leukemia cells. LIF is typically expressed at low levels in patients with cancer [116]. Experimental findings have revealed that during interval exercise, the skeletal muscle upregulates the expression of LIF mRNA via mechanisms activating STAT3 [117]. LIF modulates the inflammatory response during skeletal muscle regeneration and promotes myotube formation [118]. In contrast, TNF-like weak inducer of apoptosis (TWEAK) is activated in several patients with cancer. Human muscle biopsy studies have shown that TWEAK exerts detrimental effects on cultured muscle cells by inducing the production of multiple chemokines and proinflammatory cytokines [119]. In addition, TWEAK reduces mitochondrial content and oxidative phosphorylation and inhibits angiogenesis in the skeletal muscle [119]. Long-term exercise training prevents mammary tumor-induced muscle atrophy in rats by activating TWEAK signaling, which upregulates PGC-1α and oxidative phosphorylation-related complexes and reduces muscle inflammation [120]. Myostatin has long been recognized as a key regulator of muscle mass. Researchers have deleted myostatin in the brown adipose tissue of mice, and RNA-Seq analysis revealed signatures of mitochondrial dysfunction and inflammation after the deletion [121]. In a mouse model of lung cancer, 2 weeks of aerobic exercise (five 40–60-min sessions per week) reduced myostatin protein in the vastus lateralis [122]. Similarly, in humans with colon cancer, a 16-week resistance training program (three sessions per week) decreases the myostatin protein levels in the gastrocnemius muscle [123]. These findings indicate that resistance and aerobic exercises converge on the downregulation of myostatin in the skeletal muscle. High-mobility group box 1, a nonhistone chromatin-associated protein ubiquitous in eukaryotic cells, participates in the repair of DNA damage and maintenance of genomic stability. In addition to the abovementioned molecules, exercise regulates multiple pathways, such as parathyroid hormone-related protein and growth differentiation factor 15 [124]. These adjustments improve the dysregulated muscle immune environment caused by cancer, thereby leading to the treatment of sarcopenia.

Diabetes is another risk factor for sarcopenia. It accelerates muscle atrophy by disrupting the muscle immune microenvironment via multiple molecular pathways [125]. Insulin resistance and hyperglycemia impair mitochondrial function and oxidative metabolism, thereby promoting the development and progression of sarcopenia [126]. In addition, the accumulation of advanced glycation end-products activates their receptors, stimulating proinflammatory pathways, including NF-κB and NADPH oxidase, which together aggravate inflammation and sarcopenia [127, 128].

GLUT4 mediates glucose uptake in skeletal muscle cells. Hence, its impaired translocation reduces glucose absorption. This process elevates blood glucose levels in the skeletal muscles and worsens insulin resistance [129]. Preclinical and clinical studies have confirmed that exercise elevates GLUT4 levels on the skeletal muscle cell membrane and promotes its translocation, thereby increasing glucose uptake [130, 131]. Regular exercise training over time amplifies muscle strength in patients with diabetes and inhibits diabetes-induced systemic inflammation [132]. It also increases microvascular dilation in patients with type 2 diabetes mellitus (T2DM), strengthens microvascular sensitivity to insulin, and promotes glucose and insulin metabolism in the skeletal muscles [133].

Balanced mitochondrial fission preserves mitochondrial integrity in muscle cells [134]. In patients with T2DM, skeletal muscle mitochondria lose homeostasis and exhibit impaired function, which affect systemic metabolism [135]. High blood glucose levels disrupt mitochondrial fusion and fission, and exercise restores their dynamic balance [136]. Diabetic rats have elevated Drp1, Fis1, and MFF levels, which are associated with excessive fission, damaged mitochondria, and inflammatory pathway activation [137]. Aerobic exercise increases human skeletal muscle mitochondrial fusion proteins Mfn2 and Opa1, lowers Drp1 phosphorylation, promotes fusion, and inhibits fission [79]. Experimental studies have revealed that exercise activates PGC-1α to stimulate irisin production, thereby improving insulin sensitivity in diabetic rats. Moreover, the irisin/AMPK pathway suppresses excessive mitochondrial fission in the skeletal muscle during exercise, which reduces inflammatory responses [135, 138]. Acute, chronic, endurance, and high-intensity interval exercises promote PGC-1α nuclear translocation, where it binds to NRF1/2 to trigger mitochondrial biogenesis and mitigate insulin resistance [99, 129]. Clinical studies have confirmed that 12 weeks of aerobic exercise increases mitochondrial fusion in the skeletal muscles of patients with T2DM by enhancing the expression of Mfn1, Mfn2, and Opa1 [79].

Increased Mfn2 protects the mitochondria from mROS damage and reduces insulin resistance [139]. Exercise targets several pathways shared across distinct sarcopenia subtypes to improve physical function (Table 3). However, tailored intervention schemes are required to maximize these benefits, given the divergent baseline inflammatory and metabolic profiles of patients.

Table 3. Targets of Exercise Training in Regulating Inflammation in Aging-Related and Diabetic Sarcopenia.

Category	Aging-related Sarcopenia	Diabetic-related Sarcopenia	Cancer-related Sarcopenia
Main Characteristics	Cellular senescence [86] Immune system aging [92, 234] Adipose tissue remodeling [98] Mitochondrial dysfunction [235] Increased pro-inflammatory cytokines [92, 234] M1 macrophage polarization [236] Excessive mROS production [94] Impaired muscle regeneration [104]	Insulin resistance [237] Hyperglycemia [238] Mitochondrial dysfunction [134] Increased pro-inflammatory cytokines [126] AGEs accumulation (RAGE/NF-κB activation) [239] Excessive mROS production [240] Impaired GLUT4 translocation [241] Abnormal mitochondrial dynamics (increased fission) [136]	Deprive the nutrients required for muscle synthesis [124] Mitochondrial autophagy dysfunction [242] Excessive mROS production [124] Increased myostatin production [243]
Common Exercise Targets	Reduces pro-inflammatory cytokines [92, 234] Inhibits NF-κB pathway [104] Increases mitophagy and mitochondrial function [235] Reduces oxidative stress damage [94] Activates PGC-1α signaling to promote mitochondrial biogenesis [99]	Reduces pro-inflammatory cytokines [126] Inhibits NF-κB pathway[127, 239] Increases mitophagy and mitochondrial function [134] Reduces oxidative stress damage [240] Activates PGC-1α signaling to promote mitochondrial biogenesis [244]	Reduces pro-inflammatory cytokines [245] Inhibits NF-κB pathway [246] Increases mitophagy and mitochondrial function [247] Reduces oxidative stress damage Activates PGC-1α signaling to promote mitochondrial biogenesis [120]
Distinct Exercise Targets	Primarily focuses on reversing immunosenescence [84] Suppresses SASP [84] Reduces senescence markers (p16INK4a, p21Cip1) [248] Targets age-related redox imbalance (Nrf2/ARE pathway) [96, 249] Specifically reduces p16INK4a in CD3+ T cells [85, 250] Induces heat shock proteins [251, 252] Selectively clears senescent cells [253, 254]	Primarily focuses on improving glucose metabolism and inflammation [255] Reduces blood glucose levels [237] Increases insulin sensitivity (GLUT4 translocation) [241] Targets insulin signaling pathway [256] Modulates irisin/AMPK pathway [130] Regulates AGEs/RAGE pathway [239]	Inhibit myostatin production [243] Improve antioxidant capacity [124] Increases insulin sensitivity[257] Activates LIF signaling [116] Activates TWEAK signaling [120] Suppress myostatin and HMGB1 expression [122, 258] Inhibition of ubiquitin-proteasome system activation (atrogin-1, MuRF1) [259]

mROS: mitochondrial reactive oxygen species; AGRs: advanced glycation end products; RAGE: receptor for advanced glycation end products; NF-κB: nuclear factor kappa B; GLUT4: glucose transporter 4; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1α; SASP: senescence-associated secretory phenotype; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; AMPK: adenosine monophosphate-activated protein kinase; LIF: leukemia inhibitory factor; TWEAK: tumor necrosis factor -like weak inducer of apoptosis; HMGB1: high mobility group box 1.

3.1.6 Perspectives and Limitations

Collectively, exercise alleviates sarcopenia via diverse inflammatory pathways. Further, exercise-based combined therapies may offer a novel approach for managing sarcopenia. Specific nutrients and pharmaceuticals can work synergistically with exercise to further reduce inflammation.

β-hydroxy-β-methylbutyrate (HMB), a leucine metabolite, regulates immune responses during exercise. HMB combined with exercise suppresses the expression of inflammation-related genes in T cells [140]. Further, long-term exercise along with HMB and black ginger supplementation modifies autophagy- and mitochondria-related genes in aging mice [141]. Combined exercise and resveratrol treatments increase p-AMPK and SIRT1 levels in aged rats and decreases acetylated p53 and the Bax/Bcl-2 ratio, thereby activating the AMPK/SIRT1 pathway and inhibiting apoptosis [83, 142]. Resveratrol with exercise also reduces aging-related mitochondrial dysfunction, thereby leading to a decrease in the expression of Bad, caspase-3, and IL-6 [143]. In older adults, these interventions are safe and can improve mitochondrial function and physical performance [144]. Collectively, exercise exerts robust anti-inflammatory and anti-sarcopenic effects either alone or in synergy with nutritional supplements and pharmacological agents (Fig. 3). Notably, these combined interventions require mechanistic verification for individualized application because not all exercise combination regimens yield

synergistic effects on sarcopenia treatment. In a clinical context, glucocorticoids are frequently prescribed to manage muscular inflammation. Intermittent glucocorticoid treatment improves muscle metabolism via the PGC1α/Lipin1 axis in aging-related sarcopenia models [145, 146]. However, the combined use of exercise and glucocorticoid therapy does not further augment protein synthesis beyond the levels achieved by exercise alone [147].

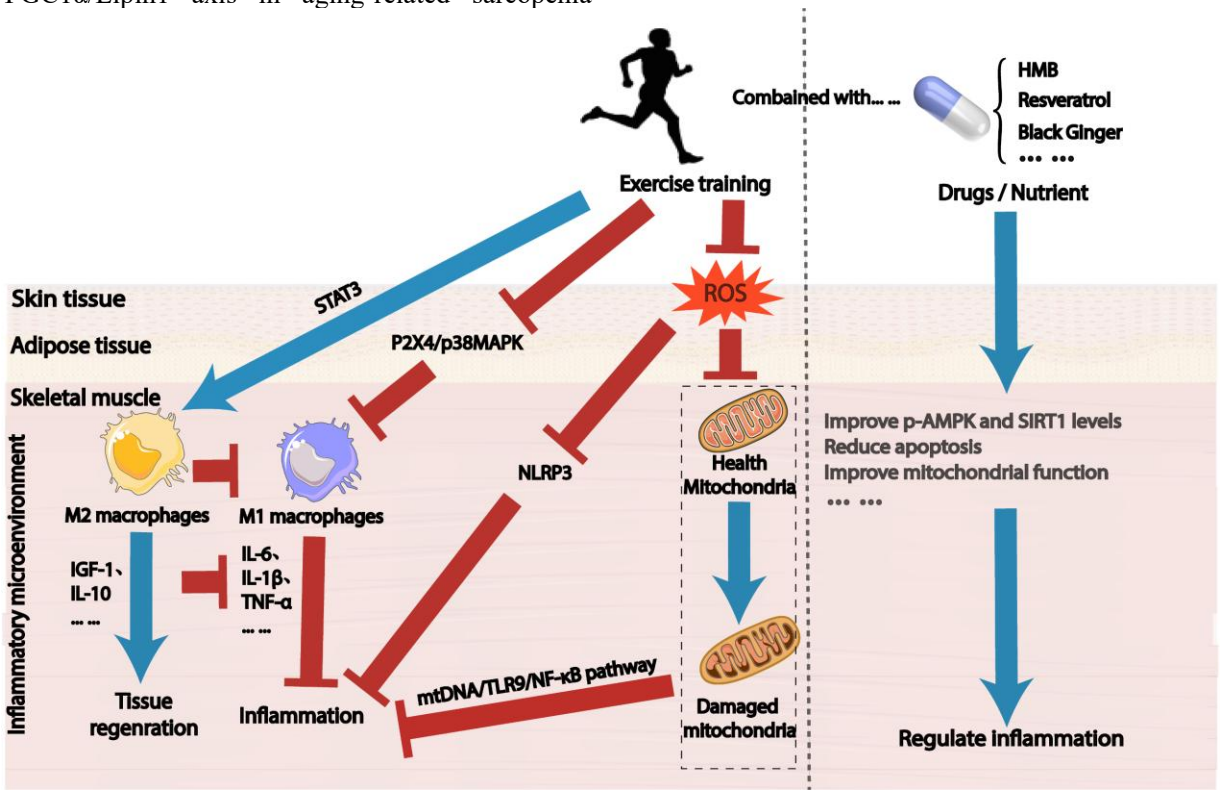

Figure 3. Exercise training regulates the immune microenvironment of skeletal muscle. Exercise induces the polarization of macrophages from the M1 to the M2 phenotype by activating STAT3 and inhibiting the P2X4/p38 MAPK signaling pathway. In addition, exercise suppresses the NLRP3 inflammasome and reduces ROS, thereby attenuating inflammatory responses, minimizing mitochondrial damage, and alleviating oxidative stress. Furthermore, supplements such as HMB and resveratrol can act synergistically with exercise to further modulate immune function, decrease apoptosis, and improve mitochondrial homeostasis.

Although exercise has a favorable efficacy in sarcopenia intervention, several limitations should be discussed. Most synergistic regimens combining exercise with nutritional adjuvants or pharmacotherapy have been validated primarily in rodent models. Large and long-term human clinical trials addressing diverse sarcopenia subtypes remain scarce. Furthermore, distinct population subgroups exhibit divergent inflammatory responses to identical training protocols. For example, aerobic exercise reduces the levels of circulating IL-6 levels in men but not in women. This finding indicates that sex regulates intervention efficacy [148]. Ethnicity also influences inflammatory responses. In particular, individuals of African ancestry often exhibit higher CRP levels than Caucasians with a similar BMI [149], indicating increased sensitivity to inflammatory stimuli that require tailored strategies for the regulation of CRP levels [150]. These variations arise from complex interactions among baseline characteristics, such as age, sex, ethnicity, metabolic status, and exercise parameters (including intensity and duration). Ultimately, these factors underscore the need for personalized exercise prescriptions for managing sarcopenia.

3.2 Nutritional Conditions and Inflammatory Microenvironment

Nutrition is essential for regulating the muscle inflammatory microenvironment in sarcopenia. In diabetes-induced cases, specific nutrients mitigate inflammation by optimizing glucose metabolism and insulin sensitivity [13]. Dietary protein intake is directly correlated with inflammatory status, and protein deficiencies exacerbate oxidative stress and wasting [151]. Polyphenols and triterpenoids found in plant proteins can lower oxidative stress and suppress

inflammatory signaling, thereby slowing the progression of sarcopenia [13]. However, clinical evidence shows that plant proteins contain fewer essential amino acids than animal proteins. Therefore, combining different protein sources is clinically recommended [152]. Further, by improving insulin sensitivity, low-carbohydrate diets can decrease circulating CRP and IL-6 levels in patients with sarcopenic obesity [153]. Thus, targeted dietary strategies remain essential for restoring muscle function.

The gut microbiota indirectly affects muscle inflammation via the gut–muscle axis [154, 155]. Probiotic supplementation could modulate sarcopenia by altering the microbial composition. These microbes metabolize fiber and protein into systemic metabolites that regulate muscle glucose and lipid metabolism, limit cholesterol synthesis, and promote lipolysis (Table 4) [156-158].

Table 4. Effects of Gut Microbiota Metabolites on the Muscle Inflammatory Microenvironment.

Metabolite	Source	Function
SCFAs	*Faecalibacterium prausnitzii*, *Bifidobacterium*, etc. [260]	Amplify glucose metabolism and IGF-1 release. IGF-1 activates the PI3K/Akt/mTOR signaling pathway, supporting muscle protein synthesis and phosphorylating FoxO to prevent muscle protein degradation [261]; Activates PGC-1α and CPT-1 expression, inhibiting muscle atrophy [262]; regulate blood glucose levels and reduce the concentrations of inflammatory factors such as IL-8, IL-17, MIP-1β, RANTES, and TNF-α in diabetic patients by increasing TGF-β1[263]
Vitamin B complex (B3, B5, B6, B7, B12), folic acid, and vitamin K	*Lactobacillus*, *Bifidobacterium*, etc.	Regulate the synthesis and metabolism of skeletal muscle [262]; prevent skeletal muscle dysfunction by preventing oxidative stress and endothelial damage caused by hyperhomocysteinemia [264]; reduce pathological causes of skeletal muscle atrophy by preventing osteoporosis [265]; plays the role of antioxidant by counteracting the formation of ROS and advanced glycation end-products [266]
Sodium butyrate	*Clostridium* clusters of the phylum Firmicutes [267]	Balance muscle protein synthesis and degradation, alleviating muscle atrophy [268]; promote autophagy by inhibiting the mTOR signaling pathway in skeletal muscle satellite cells [269]; regulate oxidative stress caused by heat stress through autophagy, maintaining skeletal muscle homeostasis [270]; amplify insulin sensitivity [271, 272]
Indole-3-lactic acid, acetoacetate, and creatine	Probiotic-M8 subspecies of *Bifidobacterium* [273]	Increase muscle function and beneficial metabolite levels; reduce the abundance of harmful bacteria and regulate metabolic pathways in the intestines of sarcopenia patients [273]; reduce the impact of inflammation on muscles [274]; reduce glucose intolerance and oxidative stress [275]
Urolithin A	*Prevotella*, *Clostridium*, *Bifidobacterium*, *Eubacterium*, and *Enterococcus* [161]	Promote muscle protein synthesis and muscle growth; heighten muscle health and performance by improving mitochondrial function and regulating autophagy [161]; reduce systemic inflammation and increase intestinal barrier function via the N-glycan biosynthesis pathway [276]

SCFAs: Short-chain fatty acids; IGF-1: insulin-like growth factor 1; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; FoxO: forkhead box O; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1α; CPT-1: carnitine palmitoyltransferase 1; IL: interleukin; MIP-1β macrophage inflammatory protein 1β; RANTES: regulated on activation normal T cell expressed and secreted; TNF-α: tumor necrosis factor α; TGF-β1: transforming growth factor β1; ROS: reactive oxygen species.

Preclinical experimental data have shown that the metabolite indole-3-propionic acid inhibits the degradation of SIRT1 ubiquitin-proteasome, which restores the ability of SIRT1 to promote PGC-1α deacetylation and nuclear translocation, thereby upregulating mitochondrial biogenesis and the expression of antioxidant genes [159]. Similarly, lactobacillus paracasei PS23 preserves the production of IL-10 and mitochondrial integrity to reduce age-associated inflammation [160]. Meanwhile, urolithin A enhances mitochondrial function and autophagy [161]. Ultimately, gut dysbiosis drives sarcopenia, and targeted probiotics provide therapeutic support via mitochondrial and immune regulation [162].

Related preclinical investigations further show that specific micronutrients also directly or indirectly regulate these inflammatory pathways. Silk peptides prevent muscle protein degradation and promote M2 macrophage polarization by regulating AKT/FoxO3a and AKT/mTOR signaling [163]. The activation of the AKT/mTOR pathway reduces muscle atrophy by suppressing oxidative stress and blocking myostatin [164, 165]. Meanwhile, AKT/FoxO3a signaling protects against apoptosis and induces skeletal muscle autophagy by increasing autophagosome formation [166, 167]. Omega-3 fatty acids further support the management of sarcopenia by lowering TNF-α and IL-6 levels and increasing IL-10 levels [168]. In addition, they reduce the erythrocyte sedimentation rate, modulate cell membrane fluidity, and

counteract the inhibition of PGC-1 and SIRT1 typically observed in metabolic disorders [133].

γ-Aminobutyric acid (GABA) regulates muscle protein metabolism via AKT/FoxO3a and AKT/mTOR signaling. GABA regulates inflammaging by optimizing the M1/M2 macrophage ratio and suppressing the overexpression of age-related COX-2 and iNOS [169]. GABA acts synergistically with IGF-1, which reduces chronic inflammation by downregulating IL-1β and IL-6. A 12-month clinical trial confirmed the safety of prolonged use of GABA [170]. Taurine exerts similar anti-inflammatory and antioxidant effects, which prevents TNF-α-induced muscle atrophy by blocking the NF-κB and TGF-β pathways [171, 172].

Despite the proven anti-sarcopenic and anti-inflammatory effects of individual nutrients like GABA and taurine, their physiological impacts vary widely across populations. Chronic psychosocial stress resulting from systemic inequity, such as racial and poverty discrimination, increases the lifelong inflammatory burden for African American, multi-generational Hispanic, and low-income populations, contributing to interethnic and generational disparities in baseline inflammatory markers and nutritional responses [173]. Consequently, anti-inflammatory nutritional strategies must account for both cultural suitability and economic accessibility. For instance, curcumin-rich turmeric serves as an accessible anti-inflammatory staple in South Asian diets [174], while plant-forward Latin American cuisines, which utilizes cumin, chili, and coriander, offer sustainable dietary anti-inflammatory approaches [175]. Because cost and unfamiliarity hinder long-term adherence to purified supplements, such as GABA or concentrated omega-3, among disadvantaged groups, culturally familiar whole foods are often more compatible with local living conditions. Nutritional interventions tailored to community resources and indigenous eating habits are more likely to deliver sustained benefits, underscoring the necessity of cross-disciplinary cooperation with local communities to develop inclusive programs that narrow inflammatory health disparities.

Microbiome analysis and genetic polymorphism testing enable precise nutritional interventions tailored based on individual health outcomes. For example, the PPAR-γ protein (encoded by the PPARG gene) regulates lipid metabolism, glucose homeostasis, and inflammation. However, its genetic variations significantly influence metabolic responses to omega-3 fatty acids. Individuals harboring specific PPARG variants exhibit greater reductions in low-density lipoprotein cholesterol and triglyceride levels after omega-3 supplementation compared with those without such variants [176].

Nevertheless, multiple translational bottlenecks still limit the application of nutritional and probiotic therapies for sarcopenia. Most existing research only captures short-term changes in inflammation and metabolism following an intervention, with observation periods typically lasting only several weeks to months. Investigators rarely conduct the prolonged follow-up necessary to record persistent therapeutic effects in patients with sarcopenic. In addition, the evidence base varies significantly across different intervention types. Data supporting single-nutrient or single-strain probiotic treatments are relatively abundant, whereas long-term clinical evidence for combined dietary regimens and multi-strain probiotic formulas remain scarce. Moreover, most exogenous probiotics are susceptible to degradation by gastric acid and digestive enzymes, leading to low in vivo survival rates and insufficient intestinal colonization [177]. Accordingly, future translational studies must address these multifaceted constraints to advance nutritional and probiotic strategies for sarcopenia management.

3.3 Small-Molecule Drug Therapy Targeting the Inflammatory Microenvironment

Drug therapies targeting the muscle microenvironment offer promising options for patients with sedentary sarcopenia. Cyclooxygenase-2 (COX-2) is upregulated by inflammation, oxidative stress, and injury [178, 179]. Celecoxib, a selective COX-2 inhibitor, improves sarcopenia by protecting mitochondrial integrity, inhibiting proteolysis, and increasing SDH-positive fibers [14]. In denervation models, celecoxib exerts anti-inflammatory and antioxidant effects by reducing the production of COX-2 and ROS and restoring redox balance by upregulating SOD1, Nrf2, GPX1, and NOX2 [14, 180]. These actions suppress the ubiquitin-proteasome and autophagy-lysosome systems, thereby enhancing muscle perfusion and motor performance [180, 181]. Clinical trials have also shown that celecoxib improves cognitive function and brain metabolism in individuals with cognitive impairment [182]. However, its long-term use (>6 months) is associated with an increased cardiovascular risk in individuals aged over 65 years [183]. Further, nonsteroidal anti-inflammatory drugs such as celecoxib and ibuprofen can inhibit satellite cell activation and delay muscle regeneration in animal experimental models, along with the risks of gastrointestinal and renal adverse effects [184, 185]. Topical formulations, such as diclofenac, are a safer alternative for sensitive patients as it decreases systemic exposure while alleviating inflammation and pain [186, 187].

In sarcopenia, GLP-1 receptor agonists could improve muscle performance by inhibiting the NF-κB pathway and suppressing the production of TNF-α and IL-

6 [188]. These agents regulate immune cell activity and limit inflammatory infiltration, providing dual metabolic and anti-inflammatory benefits. Preclinical findings have shown that semaglutide, a GLP-1 receptor agonist, increases muscle mass and strength while reducing circulating cytokines via the activation of AMPK, the inhibition of NF-κB, and mitochondrial preservation [179, 189]. Despite these benefits, clinical evidence indicates an increased risk of retinopathy complications in patients managed with semaglutide. Hence, caution must be observed in patients with pre-existing ocular conditions [190].

Emerging pharmacotherapies for sarcopenia increasingly target the IGF1-AKT-mTOR-FoxO signaling axis. For example, hesperidin reduces muscle atrophy by regulating this central pathway in aged mice [191, 192]. Similarly, sericin alleviates age-related muscle loss and suppresses chronic low-grade inflammation by targeting the same AKT/FoxO3a and AKT/mTOR signaling networks [163].

Beyond the limitations of celecoxib and semaglutide, the substantial heterogeneity observed in elderly patients with sarcopenia, specifically regarding drug tolerance, metabolic capacity, and underlying comorbidities, warrants critical acknowledgment. For instance, in a 13-week fixed-dose trial of sirolimus, a candidate anti-sarcopenia drug, effects were notably consistent. Standard weekly dosing impaired exercise-induced muscle hypertrophy in some seniors while having negligible impact on others. Furthermore, one participant developed severe pneumonia after just one dose [193].

4. Complementary and Emerging Strategies

4.1 Acupuncture and Electroacupuncture Therapy

Acupuncture can be a low-cost, highly tolerable adjunct that targets mitochondrial inflammaging via multiple routes [16]. Preclinical data indicate that this intervention suppresses the cGAS-STING-NF-κB axis, restores mitochondrial quality control, and prevents the excessive depletion of myoregulatory factor 1, thereby potentially enhancing muscle endurance [194, 195]. Concurrently, acupuncture upregulates miR-146a to inhibit the activation of NF-κB, reduces IL-1β, TNF-α, and IL-6, increases IL-10, and rebalances the Th1/Th2 equilibrium, curbing senescence-associated inflammatory cascades [196-198]. Electroacupuncture (EA) is modified type of acupuncture that uses mild electrical current stimulation with adjustable parameters for precise intensity and frequency control [199]. EA not only exerts anti-inflammatory effects that are comparable to those of traditional acupuncture but also promotes macrophage polarization toward the M2 phenotype, fostering an immune microenvironment conducive to tissue repair [200, 201]. In addition, EA upregulates the expression of SIRT1/PGC-1α and decreases PGC-1α acetylation, enhancing the production of ATP and mitochondrial biogenesis while decreasing the overexpression of calcium uniporter to ameliorate mitochondrial dysfunction, thereby arresting disease progression [72, 199, 202-204]. The anti-inflammatory efficacy of acupuncture depends on precise acupoint selection, with clinical outcomes exhibiting distinct specificity [205] (Table 5). For example, EA at ST36 engages the vagal–adrenal anti-inflammatory axis and maintains local immune homeostasis [206]. Meanwhile, BL40 stimulation protects mitochondrial function by reducing intracellular calcium overload [199].

Although 12-week randomized controlled trials have verified that acupuncture alone improves muscle mass and physical performance in sarcopenic older adults [207], most existing evidence is derived from preclinical studies. Consequently high-quality clinical data supporting these molecular signaling pathways are still lacking. Furthermore, while acupoint selections in animal experiments are adapted from the human meridian theory, further clinical investigations are required to determine whether specific acupoints exert comparable therapeutic effects in human patients.

4.2 Mesenchymal Stem Cell-Based Therapy

Current therapeutic understanding of mesenchymal stem cells (MSCs) for sarcopenia is derived primarily from preclinical animal models. These studies demonstrate that MSCs yield favorable outcomes by modulating muscular inflammation, maintaining mitochondrial function, and remodeling the aged muscle microenvironment [15]. MSCs mitigate chronic muscle inflammation by suppressing proinflammatory mediators and upregulating anti-inflammatory cytokines [208, 209]. Moreover, they remodel the muscle microenvironment by driving macrophage polarization from the proinflammatory M1 to the reparative M2 phenotype [210]. Notably, multiple preclinical observations indicate that the in vivo muscle-protective benefits of transplanted MSCs rarely rely on myogenic differentiation. Rather, they predominantly depend on the paracrine signaling molecules released into the aged muscle niche. Key secreted paracrine factors from MSCs, such as ectodysplasin-A2, thrombospondin-1, and VEGF, collectively improve microvascular perfusion, suppress senescence signaling and modulate inflammatory status in atrophic muscle tissue [211].

MSC-derived extracellular vesicles (MSC-EVs) are the pivotal paracrine effector of MSCs. MSC-EVs possess low immunogenicity, and they can serve as critical intercellular signaling mediators. Additionally, they target

and break the oxidative stress-inflammation vicious cycle that dominates the pathological progression of aged sarcopenic muscle [212]. Mechanistically, MSC-EVs ameliorate aging-related mitochondrial dysfunction and oxidative injury by inhibiting excessive ROS accumulation, activating the autophagy-lysosome pathway, and upregulating the antioxidant enzyme SOD1 [213]. Meanwhile, MSC-EVs suppress the canonical TNF-α/NF-κB inflammatory cascade to relieve muscle inflammation. They reduce local TNF-α levels, block IκB kinase phosphorylation and degradation, and inhibit NF-κB nuclear translocation, thereby preventing the excessive activation of the ubiquitin-proteasome system [214, 215]. Consistent with these molecular mechanisms, MSC-EV intervention decreases the p-NF-κB/NF-κB ratio and reduces inflammatory infiltration in atrophic muscles. Collectively, MSC-EVs alleviate aging-associated sarcopenic muscle damage via the comprehensive modulation of mitochondrial function, oxidative stress, and chronic inflammation [215].

Table 5. Mechanisms of Electroacupuncture for Sarcopenia and Related Muscle Disorders.

Author-Year	Acupoints	Intervention Parameters	Key Findings
Su et al. 2016 [200]	GB34 (Yanglingquan) + ST36 (Zusanli)	20 Hz / 1 mA; 15 min per session, every other day for 2 weeks	Up-regulates IGF-1, down-regulates myostatin, and modulates related miRNAs to counteract denervation-induced muscle atrophy and promote regeneration.
Yu et al. 2017 [277]	GB30 (Huantiao) + ST36 (Zusanli)	5 Hz / 2 mA / 0.5 ms; 30 min per session, every other day for 2 weeks	Up-regulates agrin and AChR-ε, down-regulates AChR-γ, alleviating tibialis anterior atrophy caused by sciatic nerve injury.
Chen et al. 2021 [278]	BL57 (Chengshan)	10 Hz / 0.2 ms / 1 mA; 10 min per session	Inhibits muscle C-fiber nociceptors, relieving pain.
Huang et al. 2021 [279]	GB34 (Yanglingquan) + ST36 (Zusanli)	20 Hz / 1 mA; 30 min per session	Elevates IGF1 signaling to increase protein synthesis in limb skeletal muscles.
Li et al. 2023 [199]	BL40 (Weizhong)	2/15 Hz alternating wave/2 mA; once daily, 30 min per session	Down-regulates Drp1 and MFF to maintain mitochondrial fission balance and ensure energetic homeostasis.
Guo et al. 2024 [202]	CV4 (Guanyuan) + ST36 (Zusanli) + DU20 (Baihui)	2 Hz/1 mA; 3 sessions per week, 15 min per session for 4 weeks	Activates the AMPK/Sirt1/PGC-1α axis to repair mitochondrial damage.
Shen et al. 2024 [280]	GB34 (Yanglingquan) + ST36 (Zusanli)	—	Via the IGF1/mTOR pathway alleviates CKD-related muscle atrophy and increases protein synthesis and myogenic differentiation.

IGF-1: insulin-like growth factor 1; AChR: acetylcholine receptor; Drp1 dynamin-related protein 1; MFF: mitochondrial fission factor; AMPK: adenosine monophosphate-activated protein kinase; Sirt1: sirtuin 1; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1α; mTOR: mammalian target of rapamycin; CKD: chronic kidney disease.

Nevertheless, there remains a lack of robust clinical evidence supporting the use of MSCs for the treatment of sarcopenia. Furthermore, the source of MSCs may pose a limitation to clinical translation. Bone marrow or adipose-derived stem cells collected from elderly patients with sarcopenia often exhibit age-related reductions in differentiation efficiency and proliferative capacity. However, allogeneic MSCs require an assessment of the elderly patient's immune function to avoid the risk of immune rejection. For this reason, MSC-Evs is a promising alternative for sarcopenia intervention [216].

4.3 Gene-Targeted Intervention

Beyond physical and cell-based therapeutic strategies, targeted genetic intervention may emerge as a molecular approach to alleviate mitochondrial dysfunction and mitigate persistent inflammaging in aged skeletal muscle [217]. Current preclinical studies have identified several important genetic regulators that are closely implicated in muscle mitochondrial homeostasis and inflammatory progression. Among them, SIRT5 and retinol-binding protein 4 (RBP4) are two effective targets in sarcopenia treatment [9, 218]. SIRT5, a key mitochondrial deacetylase, is critically involved in maintaining mitochondrial respiratory function, eliminating excessive ROS accumulation, and suppressing oxidative stress-triggered inflammatory activation [219]. SIRT5 exerts these protective effects by mediating desuccinylation of TBK1 at Lys137 which reduces TBK1 Ser172 phosphorylation and inhibits downstream NF-κB-related inflammatory cascades in aged muscle tissue [9]. The overexpression of lentivirus-mediated SIRT5 has been found to restore impaired mitochondrial metabolism and

alleviate muscle oxidative damage, thereby inhibiting the progression of mitochondrial inflammaging in the senescent muscle [9]. In contrast, RBP4 acts as a prosenescence and proinflammatory mediator that exacerbates muscular inflammatory infiltration and disrupts mitochondrial structural integrity under aging conditions [220]. RBP4 activates both CD4-+ T cells and macrophages through TLR4- and JNK-dependent pathways, which leads to increased secretion of inflammatory cytokines, such as IL-1β, IL-6, and TNF-α [220]. In addition, holo-RBP4 binds to its membrane receptor, STRA6, subsequently triggering the phosphorylation of JAK2 and downstream STAT3. Once activated, STAT3 upregulates the expression of the atrophy markers Atrogin-1 and MuRF1 while suppressing myogenic transcription factors MyoD and MyoG, thereby driving sarcopenic muscle loss [218]. The targeted inhibition of RBP4 relieves chronic inflammatory stress, improves mitochondrial energy metabolism, and rescues age-related muscle atrophy and functional decline. These gene-targeted manipulations enable the precise modulation of the core mitochondrial inflammaging pathway, offering novel and actionable molecular strategies for the targeted treatment of sarcopenia. Although most genetic intervention data are derived from animal models, preliminary clinical explorations are underway. For instance, an rAAV therapeutic candidate ZS112 has entered clinical trials in China (Trial registration: ChiCTR2400080864), and a corresponding AAV9-Follistatin gene therapy trial for sarcopenia is currently ongoing in Honduras (Trial registration: NCT07443826). It is worth noting that systemic administration represents a significant limitation. High-dose AAV delivered systemically tends to accumulate in the liver, potentially inducing hepatic damage. Given that elderly patients with sarcopenia often present with compromised hepatic and renal function, these risks must be rigorously evaluated whenever systemic delivery is considered.

Current clinical efforts focused increasingly on targeting inflammatory pathways to improve muscle quality, with several clinical trials currently being undertaken (Table 6). Collectively, diverse intervention strategies that focused on restraining mitochondrial inflammaging provide viable directions to slow the progression of sarcopenia and preserve skeletal muscle physiological function.

Table 6. Clinical Trials on Aging-Related and Diabetic Sarcopenia Treatment Based on Inflammatory Pathways.

Intervention Methods	Participants	Age and Sex	Clinical Trials (Status)	Country of Study	Outcome Measure
Nutritional Supplement	240	Age ≥75 years, All	NCT05324475 (Recruiting)	Switzerland	Inflammation markers; Muscle performance; Muscle mass; Muscle strength; Change in perceived health status
Isomyosamine	60	Age 60-85 years, All	NCT06942182 (Not yet recruiting)	USA	Inflammation markers; 4-meter walk test; 6-minute walk test; Grip strength
Creatine-Beta-Hydroxy-Beta-Methyl Butyrate Mixture or Guanidinoacetate Mixture	81	Age 65-80 years, All	NCT05951439 (Not yet recruiting)	Spain	Inflammation markers; Oxidative stress markers; Assessment of muscle strength and performance; Assessment of fragility
Exercise Training and Nutrition	180	Age ≥65 years, All	NCT03649698 (Recruiting)	Belgium	Inflammation markers; Change in muscle mass; Change in muscle strength; Change in markers of muscle wasting and regeneration; Change in muscle histology; Change in markers of intestinal inflammation
Concurrent Exercise Training	69	Age ≥60 years, All	NCT06545123 (Recruiting)	Portugal	Gastrointestinal Tract Microbiome and Gut-derived Metabolites; Body composition; Skeletal muscle function; Physical performance
Protein, Mobility Therapy, and Electric Stimulation	78	Age ≥60 years, All	NCT05326633 (Not yet recruiting)	USA	Change in Systemic Inflammation; Change in Muscle mass; Change in Muscle strength

Nicotinamide Riboside	144	Age 65-85 years, All	NCT04691986 (Recruiting)	USA	Serum inflammatory biomarkers; Muscle strength; Body Composition; 6-minute walk and heart rate recovery
Stem Cell	80	Age 60-80 years, All	NCT06077734 (Not yet recruiting)	Netherlands	Inflammation markers; ATP production of mesoangioblasts in vitro; Ex vivo isolated mesoangioblasts from muscle biopsy
Red Wine Polyphenols	70	Age 60-74 years, All	NCT06871384 (Not yet recruiting)	Spain	Stress Response and Mitochondria; Oxidative markers; Inflammation markers; Faecal microbial composition; Body composition; Skeletal muscle strength; Muscle mass, wasting and turnover; Biological age marker
Exercise Training	60	Age 20-80 years, All	NCT06666881 (Recruiting)	China	Inflammation markers; Muscle mass

5. Current Limitations and Risks

Targeting mitochondrial inflammaging and the inflammatory microenvironment shows a clear potential for sarcopenia management. However, several limitations and risks restrict translation into clinical practice in older adults.

While exercise is the most clinically validated strategy, its application is constrained by the physical frailty of the target population. For sedentary or bedridden seniors, high-load resistance training or HIIT poses substantial risks to bone integrity and muscle function, necessitating rigorous pre-exercise risk stratification. Furthermore, the variable inflammatory responses to training, modulated by sex and ethnic differences, require personalized exercise prescriptions to avoid exacerbating systemic stress in vulnerable individuals.

Interventions, such as nutrition and probiotics, face bottlenecks regarding sustained efficacy and safety. Clinical trials often employ insufficient observation windows, failing to account for the long-term metabolic shifts required in sarcopenia. Furthermore, the efficacy of orally administered probiotics is limited by gastric acid degradation. More critically, in elderly patients with multiple comorbidities and immunocompromised status, even standard Lactobacillus and Bifidobacterium strains carry a risk of translocation across the intestinal barrier, potentially inducing severe opportunistic infections such as bacteremia and visceral abscesses [221].

Small-molecule drugs serve as viable alternatives for patients with restricted exercise capacity, yet they demand stringent clinical monitoring due to the risks of polypharmacy. Celecoxib, for example, may impose significant cardiovascular, gastrointestinal, and renal burdens on patients already managed for hypertension or chronic kidney disease [183]. Similarly, semaglutide risks triggering retinopathy in seniors with pre-existing ocular disorders [190], and sirolimus can induce pulmonary adverse events, with outcomes further complicated by interindividual metabolic variations inherent in aged, sarcopenic patients [193]. Consequently, comprehensive baseline assessment is indispensable for safe, individualized pharmacotherapy.

Emerging modalities such as acupuncture, MSCs therapy, and gene-targeted interventions remain hindered by a lack of clinical validation. Acupuncture implementation is challenged by the lack of standardized acupoint mapping between animal and human protocols, while needle therapy itself poses risks of local tissue damage in frail seniors with compromised skin integrity [222]. Although allogeneic MSCs are considered to have better proliferative and differentiative activity than autologous stem cells from elderly individuals, they should still be used with caution in immunocompromised patients. Given that MSCs therapy for sarcopenia is primarily paracrine-mediated, MSC-EVs, which are extremely low in immunogenicity, may be a better option for treating sarcopenia. Finally, systemic AAV-based gene interventions carry significant risks of hepatic accumulation and organ toxicity. In elderly patients with impaired hepatic and renal clearance, such therapies demand rigorous preoperative screening to mitigate the risk of severe adverse events.

Taken together, these intervention-specific limitations underscore the critical needfor long-term, well-designed clinical trials that prioritize stratified research. Developing safe, anti-inflammatory therapies for sarcopenia requires a shift toward personalized, risk-aware clinical frameworks that account for the complex baseline physical conditions of the aging populations.

6. Conclusion

Sarcopenia is no longer viewed as a simple loss of both muscle mass and strength. Rather, it is now recognized as a multifactorial condition in which chronic inflammation acts as an important contributor within a mutually reinforcing cycle of cellular senescence and mitochondrial damage. This review integrates these mechanisms, focusing on how they synergistically exacerbate muscle decline. Therefore, targeting the inflammatory microenvironment is important for maintaining muscle health.

The development of specific exercise prescriptions can modulate macrophage polarization and clear senescent cells to regulate the immune environment. Further, exercise affects the different mechanisms of sarcopenia in distinct ways. Nutritional supplementation strategies can suppress inflammatory signaling via the gut–muscle axis. Pharmacological interventions can alleviate muscle atrophy and inhibit inflammation. Acupuncture or electroacupuncture improves mitochondrial integrity and immune balance via different acupoints. These approaches are progressively undergoing clinical translation. Future research should prioritize the development of integrated, multimodal intervention protocols that simultaneously encompass exercise, nutrition, pharmacotherapy, and adjunctive therapies. The treatment of skeletal muscle immune dysregulation, which is often overlooked, requires a multimodal and tailored approach in patients with sarcopenia.

Conflict of Interest

All authors declare no conflicts of interest.

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Authors' contributions

XW wrote the manuscript; SE and ZC designed figures; XT, TA and YT made tables; LF reviewed the manuscript and supervised the work

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