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Review

Myokines in Aging: A Multi-Organ Network Perspective

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ABSTRACT: Exercise training represents a well-established anti-aging intervention that counteracts the multisystem functional decline. Skeletal muscle, the primary effector of physical activity, functions as a potent secretory organ, releasing myokines and extracellular vesicles into circulation. These muscle-derived factors mediate extensive crosstalk between muscle and distant organs, thereby coordinating the multi-tissue adaptations that underline the systemic benefits of exercise. This review synthesizes current knowledge on how myokine networks counteract aging across key physiological systems—including the metabolic, cardiovascular, musculoskeletal, nervous, and immune systems—by modulating core aging-related processes such as chronic inflammation, metabolic dysregulation, and loss of tissue homeostasis. We highlight how diverse myokines converge on conserved signaling hubs to exert integrated protective effects and discuss the profound influence of sex and age on myokine action. Finally, we outline the translational potential of, and challenges to, harnessing this myokine network in clinical practice, proposing personalized exercise regimens and engineered myokine-based therapies as promising strategies for promoting healthy aging.

Keywords: aging, myokines, exercise, sarcopenia

1. Introduction

1.1 Aging as a Multidimensional Degenerative Process

Aging is a time-dependent degenerative process characterized by the accumulation of cellular and tissue damage, ultimately leading to tissue dysfunction and increased morbidity and mortality [1]. The quantification of aging has been revolutionized by multidimensional biomarkers that capture its core hallmarks across cellular, tissue, and organismal levels. At the cellular level, cellular senescence is defined by features such as irreversible cell cycle arrest, genomic instability, and mitochondrial dysfunction [2]. These changes drive tissue-level functional decline—manifested as vascular stiffening, synaptic loss, and reduced regenerative capacity—by promoting chronic inflammation and disrupting tissue homeostasis [3]. Underlying these changes are progressive alterations in the epigenetic landscape, including DNA methylation patterns and histone modifications, which serve as a fundamental molecular interface between genetic predisposition and environmental exposure throughout the aging process [4]. At the organismal level, the integration of these molecular and functional changes through advanced algorithms has given rise to powerful aging clocks. Recent large-scale proteomic studies have demonstrated that plasma protein-based clocks can accurately predict chronological age, mortality, morbidity, and organ-specific functional decline across diverse populations [5, 6].

1.2 Exercise as a Systemic Anti-aging Signal

In this context, physical exercise represents a powerful non-pharmacological intervention to counteract aging. It confers profound, systemic protection against the aging

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process [7], with benefits spanning improved metabolic homeostasis, enhanced neuroprotection, counteraction of immunosenescence, and delayed frailty [8-12]. These systemic benefits are underpinned by exercise's direct modulation of the hallmarks of aging, through mechanisms including the promotion of mitochondrial biogenesis [13], activation of autophagy, exertion of anti-inflammatory effects [14], and maintenance of telomere length [15]. For decades, a central question has persisted: how does localized physical activity produce such widespread effects? The answer is increasingly attributed to the endocrine function of skeletal muscle.

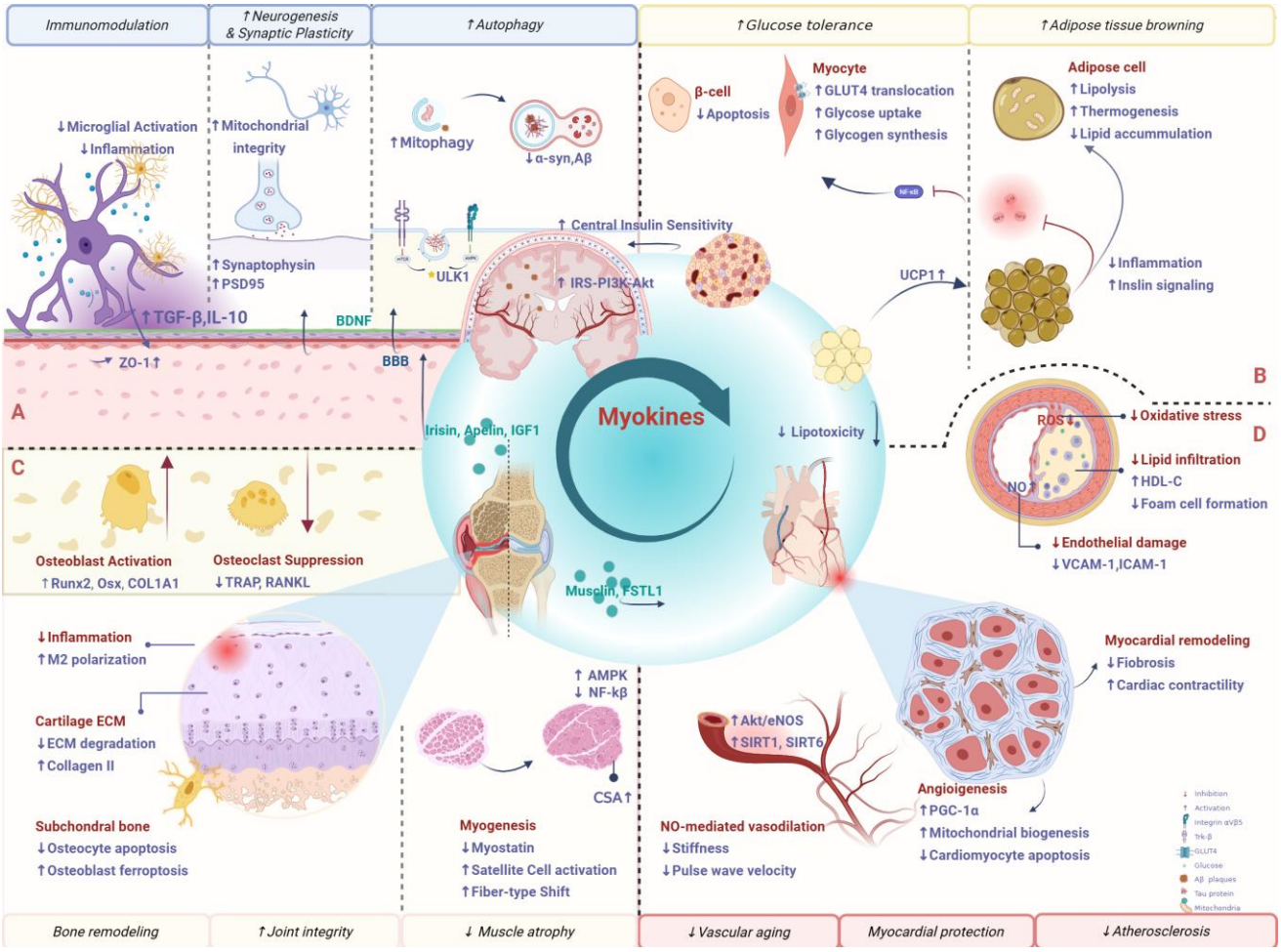

Figure 1. Myokine-Mediated Multi-Organ Crosstalk in Counteracting Aging. Skeletal muscle secretes myokines in response to exercise, establishing a systemic communication network that mitigates age-related functional decline across key organs. The figure summarizes four principal axes of this network: (A) Muscle-Brain Axis: Myokines cross the blood-brain barrier (BBB) to enhance synaptic plasticity, promote neurogenesis, clear pathological protein aggregates via autophagy, and suppress neuroinflammation by modulating microglial activation. (B) Muscle-Metabolic Axis: Myokines improve systemic metabolism by enhancing insulin sensitivity, protecting pancreatic β-cells, resolving adipose tissue inflammation, and promoting lipid oxidation and white adipose tissue (WAT) browning. This resolution of systemic metabolic stress concurrently alleviates lipotoxicity on the cardiovascular system and ameliorates cerebral insulin resistance, demonstrating cross-system synergy. (C) Muscle-MSK Axis: Myokines coordinate to maintain musculoskeletal health by stimulating muscle protein synthesis and satellite cell activity, promoting bone formation, and preserving cartilage integrity. (D) Muscle-Heart Axis: Myokines protect the cardiovascular system by improving endothelial function, reducing atherosclerotic plaque formation, enhancing mitochondrial quality in cardiomyocytes, and attenuating pathological vascular remodeling. *Icons were created with BioRender.com.* Abbreviations: BBB: Blood; ZO-1: Zonula Occludens-1; MSK: Musculoskeletal; WAT: White Adipose Tissue; CSA: Cross-Sectional Area, Ox-LDL: Oxidized Low-Density Lipoprotein; HDL-C: High-Density Lipoprotein Cholesterol; UCP1: Uncoupling Protein 1; ULK1: Unc-51 Like Autophagy Activating Kinase 1; α-syn: α-synuclein. ↓: down-regulated; ↑: up-regulated.

1.3 Skeletal Muscle as an Endocrine Organ: The Myokine Paradigm

Skeletal muscle, constituting approximately one-third of body weight, serves as the primary exercise effector organ and is increasingly recognized as a significant endocrine mediator contributing to the systemic benefits of exercise. Seminal work by Pedersen and colleagues demonstrated that contracting skeletal muscle releases cytokines, most notably interleukin-6 (IL-6), into circulation. This discovery established the revolutionary concept of "skeletal muscle as an endocrine organ" and led to coining the term "myokine" [16]. Building on this foundation, it is crucial to distinguish myokines from the broader category of exerkines (e.g., adipokines, hepatokines), which encompasses all exercise-induced signaling molecules from various tissues [17]. This review will focus specifically on myokines as the primary endocrine mediators from muscle, acknowledging that some factors like IL-6 and brain-derived neurotrophic factor (BDNF) exhibit pleiotropy and multi-tissue origins [18, 19]. During contractile activity, skeletal muscle secretes a multitude of signaling molecules, termed myokines, through both conventional secretory pathways and extracellular vesicles, thereby participating in extensive inter-tissue communication. The currently established myokine family comprises hundreds of candidate secreted proteins [20].

This review examines essential anti-aging myokines, such as IL-6, IL-15, Follistatin-like 1 (FSTL1), oncostatin M (OSM), secreted protein acidic and rich in cysteine (SPARC), BDNF, decorin (DCN), Meteorin-like protein (METRNL), myonectin (CTRP15), musclin (OSTN), irisin (FNDC5), and β-aminoisobutyric acid (BAIBA). The overall concept of myokine-mediated multi-organ crosstalk in aging is summarized in Figure 1. The following section will delve into the regulation and integrative framework of this dynamic network.

2. The Myokine Network

2.1 The Aging Muscle in Pathological States

A fundamental paradox challenges our understanding of skeletal muscle as an endocrine organ: how can a tissue that itself undergoes an inevitable decline in mass and function with age serve as a source of systemic anti-aging signals? The resolution lies in the concept of a state-dependent secretome. Sarcopenia, the age-related loss of skeletal muscle mass and function, serves as a prime exemplar of this phenomenon [21]. In this condition, the muscle's secretory profile undergoes a pathological shift—characterized by a rise in pro-inflammatory myokines and a decline in protective factors—which in turn accelerates the aging process both within muscle and in distant organs [22, 23]. It is noteworthy that interventions known to ameliorate sarcopenia, such as exercise and certain nutritional strategies, concurrently target pathways that are also engaged by myokines [24, 25]. For instance, metabolites such as β-hydroxybutyrate (β-HB) are identified to ameliorate sarcopenia by targeting core pathologies like mitochondrial dysfunction [26, 27]. The convergence of these independent lines of evidence suggests that the normalization of the dysregulated myokine network is a central event in counteracting sarcopenia, positioning it as both a mediator of intervention benefits and a direct executor of rejuvenation.

2.2 Regulation and Translational Potential of the Myokine Network

In direct opposition to the pathological remodeling in sarcopenia, physical exercise serves as the most potent physiological stimulus to reprogram the myokine network towards a health-promoting, youth-associated state. As the body's largest effector organ, skeletal muscle releases myokines and metabolites—both in free form and encapsulated within muscle-derived extracellular vesicles (Mu-EVs)—which mediate systemic homeostasis. These factors possess a dual translational identity: they are functional mediators that impede cardiovascular, neurological, and oncological progression, as detailed in Table 1 [28], and they serve as sensitive biomarkers for diagnosing and stratifying age-related diseases [29-31]. This dual identity significantly elevates the translational value of the myokine network.

Crucially, the pattern of myokine secretion is highly dependent on exercise modality, as summarized in Table 2. Endurance exercise predominantly activates the AMPK-PGC-1α axis, promoting the release of myokines like BDNF and apelin. In contrast, resistance exercise primarily signals through mTOR pathways, favoring the secretion of myokines such as IL-15 [32]. Notably, several myokines demonstrate broad responsiveness to both endurance and resistance exercise, whereas others exhibit more modality-specific induction. It is also important to note that the distinction between signaling pathways is not absolute. Instead, significant crosstalk exists, and the response is context-dependent, influenced by factors such as exercise intensity and individual physiological status [33], and specific disease contexts. For example, musclin levels increase acutely after moderate-intensity continuous training (MICT) but decrease chronically following resistance training in patients with type 2 diabetes (T2DM) [34]. Collectively, the available evidence suggests that a combination of endurance and resistance exercise may elicit a broader and

more diverse myokine response compared to either modality alone [35], thereby supporting the concept that the myokine network serves as a key mechanism through which exercise promotes healthy aging. This modality-specific secretion pattern underscores the potential for designing tailored exercise regimens to optimize systemic benefits

Table1. Overview of interorgan communication mechanisms mediated by myokines.

Myokine	Target Tissue/Organ	Function	Signaling Pathway/ Mechanism	Model & Approach	Phenotypic Outcomes	Ref.
BDNF	**Brain**	Neuroprotection	↑ sAPPα production	Preclinical (KO, supplementation)	↓ Aβ pathology	[145]
	Muscle	Mitochondrial quality control	↑ CaMKK2-PPARδ	Preclinical (KO, exercise)	↓ Fat accumulation, ↓ mitophagy defects	[66]
		Lipid metabolism	↑ PRKAA/AMPK-PINK1-PRKN/Parkin	Preclinical (KO)	↓ Insulin resistance	[67]
BAIBA	**Intervertebral Disc**	Intervertebral disc protection	↑ AMPK, ↓ NF-κB	Human, Preclinical (Exercise, supplementation)	↓ ECM degradation, ↓ PANoptosis	[98]
	Bone	Anti-oxidative stress	↑ MRGPRD-dependent	Preclinical (Muscle contraction)	↑ Osteocyte viability, ↓ Bone loss	[94]
	Muscle	Metabolic improvement	↑ AMPK-PPARδ, ↓ NF-κB	Preclinical (Supplementation)	↓ Insulin resistance	[56]
	Adipose tissue, liver	Lipid metabolism	PPARα-mediated mechanism	Human, Preclinical (Exercise)	↑ WAT, ↑ hepatic fatty acid β-oxidation	[192]
	Vasculature	Vascular protection	↑ LKB1/AMPK/SIRT1	Preclinical (Supplementation)	↓ VSMC proliferation/migration	[113]
Musclin	**Heart**	Cardioprotection	↑ CNP/NPR-B	Human, Preclinical (KO, OE, tissue analysis)	↑ Cardiomyocyte contractility, ↓ Fibroblast activation	[118], [119]
		Cardioprotection	↑cGMP/PKGI/CREB/PGC1α	Preclinical (Exercise, supplementation)	↑ Mitochondrial biogenesis, ↓ Infarct size	[216]
	Muscle	Muscle homeostasis regulation	↑ AKT/FoxO3a/FILIP1L	Preclinical (Exercise, supplementation)	↑ FAPs apoptosis, ↓ ECM remodeling	[217]
METRNL	**Heart**	Cardioprotection	↑ cAMP/PKA/SIRT1	Human, Preclinical (Exercise, supplementation)	↑ LVEF, ↓ Oxidative stress	[122], [194]
			↑ LKB1/AMPK/ULK1	Preclinical (Supplementation)	↑ Autophagy, ↓ Cardiac hypertrophy, ↓ Oxidative stress	[218]
		Angiogenesis	↑ KIT Receptor Activation	Preclinical (Supplementation)	↑ KIT+ endothelial proliferation	[123]
	Muscle	Anti-inflammation	↑ AMPK-PPARδ	Preclinical (Supplementation)	↓ NF-κB/IL-6/TNFα, ↑ FAO	[57]
	Pancreas	Glucose metabolism regulation	↑ Wnt/β-catenin	Preclinical (Supplementation)	β cell (↑ proliferation, ↓ apoptosis), ↓ Body weight	[219]
	Intervertebral Disc	Lipid metabolism	↑ PPARα-CPT1A	Human, Preclinical (Exercise, supplementation)	↓ Lipid accumulation, ↓ ECM degradation	[97]
Irisin	**Brain**	Mitochondrial dynamics and morphology	↑ Akt/ERK1/2, ↑ SIRT1/PGC1α/TFAM	Human, Preclinical (Exercise, supplementation)	↑ Motor function, ↓ Neurodegeneration, ↓ Microglial senescence	[167], [157]
	Gut-Brain Axis	Anti-inflammation	↓ TLR4/MyD88	Preclinical (Exercise, supplementation)	↓ Insulin resistance, ↓ Cognitive decline	[182]
	Bone	Osteoblast activation	↑ αVβ5/ERK/p38, ↓ TβRII/Smad2/3, ↓ HDAC4/5	Preclinical (KO, supplementation)	↑ Bone mass/strength	[220], [221]
	Vasculature	ER Calcium homeostasis regulation	↑ AMPK, ↓ p38	Preclinical (Supplementation)	↓ VSMC remodeling, ↓ Hypertension	[222]
		Vascular protection	↑ DnaJb3/Hsp40/SIRT6 stabilization	Human, Preclinical (Exercise, KO and human study)	↓ Arterial stiffness	[112]

	Heart	Antioxidant, Anti-apoptotic, Anti-inflammation	AKT/GSK3β/FYN/Nrf2 axis, ↑ GLP-1R/AMPKα	Preclinical (Overexpression, supplementation)	↓ Oxidative stress, ↓ Apoptosis, ↓ Heart remodeling	[223], [224]
	Adipose Tissue	Lipid metabolism	↑ AMPK-UCP1	Human, Preclinical (Supplementation)	↑ WAT browning, ↑ Thermogenesis	[225], [226]
	Muscle	Cytoprotection	↑ AMPK-insulin receptor	Preclinical (Supplementation)	↓ Apoptosis, ↓ Insulin resistance	[47]
		Metabolic dysfunction regulation	-	Human, Preclinical (KO, supplementation)	↑ Grip strength, muscle weights, fiber size	[227]
FSTL1	**Heart**	Cardioprotection	↓ MsrB2/Parkin	Preclinical (Supplementation)	↑ LVEF/LVFS, ↓ Pathological mitophagy	[114]
			↑USP10/Notch1	Preclinical (Overexpression)	↓ Fibrosis	[121]
		Angiogenesis	↑ DIP2A-Smad2/3-VEGF	Preclinical (KO, exercise, supplementation)	↑ HUVEC proliferation	[228]
	Adipose Tissue	Lipolysis	↑ DIP2A-cGMP-PKA-HSL	Human, Preclinical (Exercise)	↑ Glycerol release, ↓ PPARγ/C/EBPα	[229]
Apelin	**Muscle**	Mitochondriogenesis	↑ APLNR-AMPK-PGC1α	Human, Preclinical (KO, Overexpression)	↑ Muscle mass/strength	[230]
		Muscle regeneration	↑ Tead1-Apln-Aplnr	Human, Preclinical (KO, supplementation)	↑ Endothelial remodeling	[78]
	Brain	Neuroprotection	↑ Autophagy Pathway	Preclinical (Supplementation)	↑ LC3B-II/Beclin1, ↓ p62	[153]
Fibcd1	**Muscle**	Anti-cachectic myoprotection	↑ ERK signaling	Preclinical (Supplementation)	↑ Myofiber size	[231]
CLCF1	**Muscle, Bone**	Muscle/bone metabolism	↑ AKT/mTOR/S6K, ↑ STAT3-Runx2, ↓ STAT1-NFATc1	Preclinical (Exercise)	↑ Glycolysis, ↑ Osteogenesis, ↓ Osteoclast activity	[185]

This table summarizes the target tissues, biological functions, underlying signaling pathways, experimental models, and phenotypic outcomes of key myokines. Abbreviations: KO, knockout; OE, overexpression; ECM, extracellular matrix; VSMC, vascular smooth muscle cell; LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; sAPPα, soluble amyloid precursor protein α; Aβ, amyloid-beta; PANoptosis, pyroptosis-apoptosis-necrosis; FAPs, fibro-adipogenic progenitors; MRGPRD, Mas-related G protein-coupled receptor D; ↑, increased or activated; ↓, decreased or inhibited.

2.3 An Integrative Anti-Aging Framework via the Myokine Network

We propose that the myokine network functions as a central processor, translating contractile activity into systemic anti-aging signals [36]. Its protective role manifests through a dual program: a systemic recalibration of metabolic and inflammatory milieu, which mitigates aging drivers like inflammaging [37, 38], and a local reinforcement of tissue resilience and repair, which directly counters sarcopenia and functional decline [39]. This framework is dynamically regulated through epigenetic reprogramming. Exercise-induced reactive oxygen species (ROS) reverse age-related epigenetic alterations, thereby remodeling the myokine secretome to combat aging [40]. This positions the epigenetic regulation of the myokine network as a central mechanism through which exercise counteracts aging at a molecular level.

Equipped with this integrative framework of core cytoprotective programs, we will now explore how the myokine network executes these strategies across different organ systems.

3. Metabolic-Endocrine System

The metabolic-endocrine system is a primary site where the core cytoprotective programs orchestrated by myokines converge to counteract aging. These programs, particularly metabolic recalibration and the resolution of inflammaging, are critical in mitigating the age-related decline in glucose and lipid homeostasis [41], which underlies pathologies such as T2DM, obesity, and nonalcoholic fatty liver disease (NAFLD). Myokines, including IL-6 [42], irisin, METRNL, and FGF21 [43], have been implicated in preserving metabolic homeostasis. These myokines function not merely by alleviating symptoms but by directly targeting core metabolic disturbances, thereby retarding disease progression.

3.1 Glucose Metabolism

Aging is characterized by a state of chronic low-grade inflammation and ectopic lipid accumulation, which exacerbates insulin resistance (IR). Exercise-induced myokines counteract this decline through a coordinated, multi-tiered defense strategy.

Myokines provide a critical defense for pancreatic β-cells, which are highly vulnerable to inflammatory damage. This protection is achieved through both anti-apoptotic and anti-inflammatory actions, as seen with

angiogenin (ANG) and osteoprotegerin (OPG) [44], and by directly promoting insulin secretion and cell survival via decorin and BDNF signaling [45, 46]. Furthermore, myokines like irisin enhance systemic insulin sensitivity by activating pathways involving PGC-1α [47, 48], thereby reducing the metabolic stress on β-cells.

Beyond that, myokines directly ameliorate the chronic low-grade meta-inflammation, characterized by immune cell infiltration in adipose tissue and liver, which underpins age-related insulin resistance. The context-dependency of IL-6 is pivotal. Unlike its detrimental chronic elevation, the acute, exercise-induced IL-6 surge exhibits potent anti-inflammatory properties [49], suppressing TNF-α while upregulating IL-1Ra and IL-10 [50]. This anti-inflammatory shift is corroborated by a training study in women with insulin resistance, where increased serum IL-6 correlated with improved outcomes [51]. Similarly, irisin alleviates metabolic syndrome by suppressing adipose tissue inflammation and inducing M2 macrophage polarization [52], and elevated myonectin has been linked to improved insulin sensitivity in obese women [53].

Table 2. Differential induction of myokines by various exercise regimens.

Myokine	Exercise Intervention	Key Findings	Study Design	Ref.
Irisin	Resistance Training	↑ Marked increase post-exercise; response greater than endurance exercise alone.	Chronic	[232]
	HIIT	↑ Intensity-dependent increase.	Acute	[233], [234]
BDNF	HIIT & MICT	↑ Consistently increased by both MICT and HIIT.	Chronic	[235], [236]
	SIT	↑ Plasma levels increased in an intensity-dependent manner.	Acute	[237]
SPARC	MICT	↑ Significantly increased at 60-70% VO_2 peak but not at 40% VO_2 peak.	Acute	[238], [239]
BAIBA	MICT	↑ Consistently increased plasma levels.	Chronic	[240]
METRNL	HIIT	↑ Increased mRNA after acute and chronic HIIT.	Acute & Chronic	[241]
	Resistance Training	↑ Serum level increased after eight-week training in men with T2DM.	Chronic	[242]
Musclin	MICT	↑ Serum levels significantly increased during exercise.	Acute	[119]
	Resistance Training	↓ Muscle expression significantly decreased in a T2DM rat model.	Chronic (Preclinical)	[34]
Apelin	MICT & HIIT	↑ Serum levels increased in middle-aged and older adults, and T2DM patients.	Acute & Chronic	[109], [110], [243]
	SIT	↑ Significantly increased following acute SIT.	Acute	[244]
	Resistance Training	↑ Significantly increased after 12-week training.	Chronic	[245]
FLST1	SIT	↑ Significantly increased following acute SIT.	Acute	[244]
IL-6	MICT	↑ Significantly increased after 30 minutes exercise.	Acute	[246]
IL-15	Resistance Training	→ No significant change in resting plasma concentration after a 12-week program.	Chronic	[245]

This table synthesizes findings from various studies, reporting the directional change (increase: ↑, decrease: ↓, no change: →) in circulating levels or tissue expression of selected myokines in response to acute or chronic exercise. Abbreviations: brain-derived neurotrophic factor (BDNF), secreted protein acidic and rich in cysteine (SPARC), β-aminoisobutyric acid (BAIBA), meteorin-like protein (METRNL), fibronectin domain-containing protein 5/irisin (FDNC5/Irisin), follicistatin-like 1 (FSTL1), interleukin-6 (IL-6), interleukin-15 (IL-15), type 2 diabetes mellitus (T2DM), high-intensity interval training (HIIT), moderate-intensity continuous training (MICT), and sprint interval training (SIT).

Concurrently, a distinct set of myokines enhances insulin signal transduction. Myokines such as SPARC [54] and IL-15 [55] improve skeletal muscle glucose tolerance, while BAIBA [56] and METRNL [57] enhance insulin signaling and attenuate inflammation. The novel myokine ATPase inhibitory factor 1 (IF1) uniquely engages multiple signaling pathways to regulate glucose metabolism [58]. IL-6 also exerts potent short-term insulin-sensitizing effects [59] by enhancing glucagon-like peptide-1 (GLP-1)-mediated insulin secretion [60] and promoting glucose transporter 4 (GLUT4) translocation [61].

In summary, by safeguarding the insulin source, resolving underlying inflammation, and enhancing tissue responsiveness, these myokines form a synergistic, exercise-induced endocrine network that robustly counteracts age-related glucose metabolism dysregulation.

3.2 Lipid Metabolism

Aging impairs adaptive thermogenesis and promotes lipid accumulation. Myokines counter these changes by

promoting thermogenesis, enhancing fatty acid oxidation, and modulating cholesterol homeostasis.

A key strategy is the activation of transcriptional programs that drive energy expenditure. Irisin is a potent inducer of white adipose tissue (WAT) browning and thermogenesis [62, 63], while concurrently suppressing lipogenesis [64], a process further confirmed to be mediated by its extracellular vesicle form [65]. BDNF promotes fatty acid oxidation and is critically involved in maintaining mitochondrial quality control in aged muscle [66, 67].

Beyond transcriptional regulation, myokines directly modulate lipid fluxes. IL-6 functions as a novel lipolytic hormone [68] that stimulates free fatty acid release from adipose tissue, and myonectin enhances fatty acid uptake into tissues [69]. Exercise restores the expression of biglycan (BGN), a novel myokine whose levels decrease with age in both human and murine models. BGN effectively attenuates senescence-induced lipid accumulation and ROS generation [70]. METRNL and irisin also play direct roles in modulating cholesterol homeostasis, with METRNL enhancing reverse cholesterol transport [71] and irisin contributing to dyslipidemia management [72].

The myokine network demonstrates remarkable functional nuance, as the net metabolic outcome often depends critically on the pathophysiological context. This context-dependency is exemplified by musclin and IL-6. In obesity, musclin suppresses beige adipocyte thermogenesis [73] and can impair insulin sensitivity in skeletal muscle [34], contrasting with its potential benefits in other settings. Similarly, the role of IL-6 is dualistic. While its chronic, systemic elevation is pathological, genetic studies confirm that exercise-induced, muscle-derived IL-6 is indispensable for mediating benefits such as adipose tissue lipolysis and anti-inflammatory signaling [74, 75].

Thus, through an integrated and context-sensitive strategy, myokines prevent and ameliorate age-related metabolic syndromes by coordinately modulating glucose homeostasis, lipid flux, and chronic inflammation.

By coordinately regulating glucose and lipid metabolism while quenching meta-inflammation, the myokine network effectively mitigates shared risk factors that propel both cardiovascular and neurodegenerative pathologies. This foundational mitigation sets the stage for more direct, organ-specific protective actions to take full effect.

4. Musculoskeletal System

The assessment of musculoskeletal aging is being refined by tools like the epigenetic clock MskAge, which quantifies biological age with high precision [76]. In this context, sarcopenia is not only a consequence but also a driver of multisystem aging, largely mediated by a dysregulated secretory profile from skeletal muscle. This pathological shift in myokine secretion disrupts tissue homeostasis, accelerating the core pathologies of sarcopenia, osteoporosis, and osteoarthritis. Here, we delineate the mechanisms through which a therapeutically restored myokine network coordinates local repair, upholds structural integrity, and resolves inflammation.

4.1 Tissue Turnover

The progression of sarcopenia and osteoporosis shares common pathophysiological mechanisms and is fundamentally driven by a shift in the balance between anabolism and catabolism [77]. A network of myokines acts as a key countermeasure to this age-related imbalance through complementary anabolic stimulation and catabolic suppression.

To promote anabolism, the apelin/APJ system attenuates age-related muscle atrophy by restoring compromised AMPK signaling, thereby enhancing mitochondrial function, activating satellite cells, and promoting fiber hypertrophy [78]. The clinical relevance of this pathway is underscored by the finding that vitamin D3 supplementation's benefits on muscle strength and mass are mechanistically linked to apelin/APJ activation [79]. It is important to note, however, that the efficacy of this compensatory mechanism may be limited in advanced sarcopenia by the profound pro-inflammatory microenvironment. Additionally, muscle-derived BDNF promotes regeneration and counters pathological fiber-type shifts by activating satellite cells [80], while Mu-EVs deliver miR-140-5p to regulate satellite cells, facilitating skeletal muscle repair and remodeling [81].

In bone, irisin exerts potent anabolic effects through multiple pathways. It promotes osteoblast proliferation, inhibits osteoblast ferroptosis by upregulating ferroportin [82], and modulates bone remodeling [83]. Emerging evidence suggests irisin directly influences osteocytes to modulate sclerostin secretion [84]. Furthermore, the transfer of LDHA-rich Mu-EVs to bone marrow stromal cells enhances glycolytic flux and osteogenic gene expression [85, 86]. While this reveals a novel mechanism for exercise-induced bone formation, the relative contribution of this pathway compared to circulating myokines like irisin remains to be quantified. Interestingly, even in the absence of exercise, pharmacological inhibition of HDACs promotes osteogenesis by increasing Mu-EVs containing miR-873-3p [87], highlighting the therapeutic potential of targeting this axis.

To suppress catabolism, myokines target key negative regulators. The myostatin pathway represents a

prime target, with the myokine decorin serving as its natural endogenous inhibitor [88]. While pharmacological inhibition of myostatin has shown promise in increasing muscle mass, clinical trials reveal inconsistent functional benefits, underscoring the complexity of this approach [89, 90]. This limitation may be rooted in a fundamental oversight: myostatin exhibits an evolutionarily conserved circadian rhythm, and the loss of this temporal regulation—rather than just the absolute protein level—appears to be a critical pathological driver [91]. In contrast, lifestyle interventions such as endurance exercise [92] and high-dose vitamin D supplementation [93] can suppress myostatin expression, with exercise potentially leveraging this circadian dimension. Similarly, BGN counteracts the expression of atrophy-related genes and mitigates muscle mass loss [70].

4.2 Structural Integrity

The functional integrity of musculoskeletal tissues is dependent on the health of their structural components, particularly the extracellular matrix (ECM). Myokines play crucial roles in maintaining this structural scaffold across bone, cartilage, and intervertebral discs.

In bone, L-BAIBA protects osteocytes from ROS-induced apoptosis and maintains mitochondrial integrity [94]. It should be noted that the potency of this protection is influenced by sex and age, a theme explored in Section 9. Nevertheless, L-BAIBA shows therapeutic potential for postmenopausal osteoporosis by suppressing osteoclastogenesis [95].

In articular cartilage and intervertebral discs, where the balance between ECM synthesis and degradation determines tissue integrity, myokines provide essential regulation. Irisin upregulates collagen II synthesis while inhibiting the catabolic enzyme MMP-13, thereby preserving subchondral microarchitecture [96]. Similarly, METRNL prevents lipid accumulation in nucleus pulposus cells via the PPARα-CPT1A pathway, safeguarding against ECM degradation and cellular senescence [97]. Complementing these actions, L-BAIBA promotes ECM synthesis and inhibits NPC apoptosis, further slowing intervertebral disc degeneration (IVDD) progression [98].

4.3 Inflammation and Cellular Senescence

Beyond systemic meta-inflammation, the musculoskeletal system faces distinct inflammatory challenges driven by local tissue damage, cellular senescence, and mechanical stress. Myokines mediate potent anti-inflammatory and anti-senescent effects across these tissues.

In aged muscle, sterile inflammation driven by the NLRP3 inflammasome is a key driver of pathology [99]. This can be counteracted by C1q/TNF-related protein 9 (CTRP9), whose expression declines with senescence. CTRP9 promotes the selective autophagic degradation of NLRP3, mitigating the chronic inflammatory state in aged muscle [100]. In osteoarthritic joints, myokines counteract the catabolic and inflammatory cascade that degrades articular cartilage. Irisin alleviates chondrocyte inflammation and ECM degradation by inhibiting PI3K/Akt/NF-κB cascade activation and ameliorating chondrocyte pyroptosis [101]. METRNL also directly targets the NLRP3 inflammasome, suppressing its activation and associated inflammatory pathways, thus protecting chondrocytes from inflammation and pyroptosis [102]. This convergence on critical inflammatory nodes underscores a key organizational principle of the myokine network, the details of which are explored in Section 8.1.

5. Cardiovascular System

The protective benefits of the myokine network for the cardiovascular system are mediated through a combination of metabolic recalibration, inflammaging resolution, and targeted repair programs. Myokines thereby ameliorate the triad of aging-driven dyslipidemia, vascular stiffening, and myocardial dysfunction [103].

5.1 Vascular Protection

Myokines safeguard the vasculature through complementary actions on the endothelium and the surrounding vascular wall. At the frontline, myokines protect the endothelium and combat the chronic inflammatory process of atherosclerosis. Irisin confers multifaceted atheroprotection by ameliorating endothelial dysfunction, attenuating lipid-induced vascular inflammation, and regulating lipid homeostasis [104]. Within the atherosclerotic plaque, it further suppresses endothelial apoptosis [105], stimulates angiogenesis [106], and promotes endothelial proliferation [107]. BAIBA confers atheroprotective effects by suppressing the expression of VCAM-1 and MCP-1 in endothelial cells, thereby impairing the monocyte recruitment and macrophage accumulation within the developing plaque [108].

Beyond the endothelium, myokines directly target vascular stiffening and pathological remodeling. In middle-aged and older adults [109] and patients with type 2 diabetes [110], aerobic exercise elevates plasma apelin and NOx, supporting a role for apelin in reducing arterial stiffness. Irisin mitigates vascular aging by suppressing the expression of cell adhesion molecules (CAMs) and pro-inflammatory cytokines [111]. Mechanistically, irisin-enriched EVs delay vascular smooth muscle cell

(VSMC) senescence by enhancing the stability of the longevity protein SIRT6 [112]. Similarly, in hypertension, BAIBA mediates its protective effects against vascular oxidative stress, inflammation, and fibrosis via SIRT1, leading to attenuated pathological remodeling [113].

5.2 Myocardial Support

The aging heart's resilience requires sustained metabolic fitness and robust capacity for repair. The myokine network provides integrated support across this functional spectrum.

To sustain cardiomyocyte viability, myokines optimize energy metabolism and mitochondrial quality. FSTL1 modulates mitochondrial quality through autophagy regulation [114], while exercise-generated BAIBA improves mitochondrial function and reduces apoptosis via AMPK phosphorylation [115]. MG53 preserves mitochondrial integrity through cardiolipin binding [116]. Its elevated serum levels in acute coronary syndrome patients position it as a prognostic biomarker, yet its therapeutic translation requires further validation of dosing and a deeper understanding of its mechanisms [117].

In parallel to sustaining basal viability, myokines activate repair programs to maintain cardiac structure and function after insult. Musclin enhances C-type natriuretic peptide (CNP)/NPR-B signaling to improve contractility and suppress fibroblast activation [118]. In humans, exercise-induced musclin potentiates natriuretic peptide signaling by preventing ANP degradation and interacting with NPR-C expression [119]. FSTL1 exhibits protection by improving myocardial energetics and ventricular function in clinical heart failure [120], while also attenuating fibrotic remodeling [121]. METRNL orchestrates repair through dual pathways: activating the cAMP/PKA/SIRT1 for metabolic protection [122] while serving as a ligand for the receptor tyrosine kinase KIT to drive post-MI angiogenesis [123]. Additionally, myonectin has shown cardioprotective potential in acute myocardial ischemia models [124], further underscoring the therapeutic value of the myokine network.

Collectively, these findings illuminate a central paradigm in myokine biology: their dual identity as both functional mediators of cardiovascular benefits and circulating biomarkers of physiological and pathological states. This very duality, however, presents a fundamental challenge for clinical translation: distinguishing causative protective actions from correlative biomarker signals is paramount for developing myokine-based diagnostics and therapies. Future research must disentangle this complexity to fully harness the therapeutic potential of the myokine network in combating cardiovascular aging.

6. Immunosenescence

While preceding sections have detailed myokine-mediated inflammation resolution within specific organs, the immune system represents the central orchestrator of systemic inflammaging. Immunosenescence, its functional decline, is thus a primary target. The myokine network counteracts this by deploying a dual strategy: resolving the chronic inflammatory milieu and rejuvenating immune cell function, thereby restoring systemic immune homeostasis and surveillance [125].

6.1 Immune Regulation

A growing body of evidence demonstrates that exercise-induced myokines are pivotal mediators counteracting aging-driven immunological decline by directly reprogramming the function and phenotype of immune cells [38]. Mechanistic insights reveal how myokines coordinate innate and adaptive immunity. Regarding innate immunity, myokines act to curb excessive inflammation and bolster frontline defense. For instance, IL-15 [126] and exercise-induced IL-6 act synergistically to enhance natural killer (NK) cell cytotoxicity and trafficking [127], boosting diminished immune surveillance. IL-6 further induces an anti-inflammatory response through IL-10 secretion and IL-1β inhibition [128]. Concurrently, myokines like OSM and irisin instruct peripheral macrophages to shift toward the anti-inflammatory M2 state [129, 130]. The protective role of irisin extends to subcellular homeostasis, as it alleviates ox-LDL-induced endoplasmic reticulum stress (ERS) and subsequent apoptosis in macrophages [131]. Furthermore, irisin significantly inhibits the formation of neutrophil extracellular traps (NETs), thereby neutralizing a potent source of tissue damage [132].

Simultaneously, myokines directly promote tolerance and precision in the adaptive immune system. A key mechanism is the enhancement of regulatory T cell (Treg) function. Irisin enhances the transcriptional activity and suppressive function of Tregs by upregulating Foxp3 expression [133]. In a similar vein, METRNL modulates $CD4^+$ T cell differentiation and attenuates inflammation-driven tissue damage in model systems [134]. Completing this picture, Mu-EVs serve as another critical class of messengers. Exercise-responsive Mu-EVs containing miR-29a-3p orchestrate tumor immune micro-environment (TIME) reprogramming by inhibiting collagen expression, thereby enhancing immune cell infiltration and immunotherapy efficacy in several cancer types [135].

The immunomodulatory functions of myokines described above, which involve recalibrating both innate and adaptive immunity, provide the mechanistic basis for

the inflammation-resolving effects observed in metabolic, musculoskeletal, and neural tissues. Collectively, these findings illustrate an emerging paradigm in which skeletal muscle, as an active endocrine organ, fine-tunes immune homeostasis through a network of myokines. By simultaneously restraining innate immune overactivation and promoting adaptive immune regulation, this myokine network represents a critical mechanism for counteracting age-related chronic inflammation and functional immune decline.

6.2 Cancer Prevention

The capacity of myokines to recalibrate systemic immunity, as detailed above, directly dismantles a key permissive factor for cancer: the aged and inflamed microenvironment. By quenching inflammaging and rejuvenating immune surveillance, myokines indirectly create a tumor-suppressive landscape. Furthermore, a compelling body of evidence demonstrates that myokines can directly target tumor cell viability and metastasis.

Irisin inhibits proliferation in various cancer models, counteracts invasion in glioblastoma, and suppresses the epithelial-mesenchymal transition (EMT)—a key step in metastasis [136-138]. OSM induces cancer cell cycle arrest [139], and SPARC promotes apoptosis in colorectal cancer [140]. Additionally, decorin can inhibit tumor growth via blockade of the Met/EGFR pathway [141].

Critically, this pre-clinical framework is now substantiated by human evidence. A 12-week exercise intervention in breast cancer survivors significantly elevated serum levels of SPARC and OSM. Most importantly, post-intervention serum directly inhibited the growth of triple-negative breast cancer cells in vitro [142]. This functional evidence firmly links exercise-induced myokines to the creation of a tumor-suppressive environment in humans.

Thus, myokines emerge as key mediators that suppress tumorigenesis through an integrated strategy, combining indirect immunomodulation with direct oncosuppressive activity. This multifaceted action, summarized in Figure 2, underscores the vital immunoregulatory, anti-aging, and metabolic roles of the skeletal muscle endocrine system.

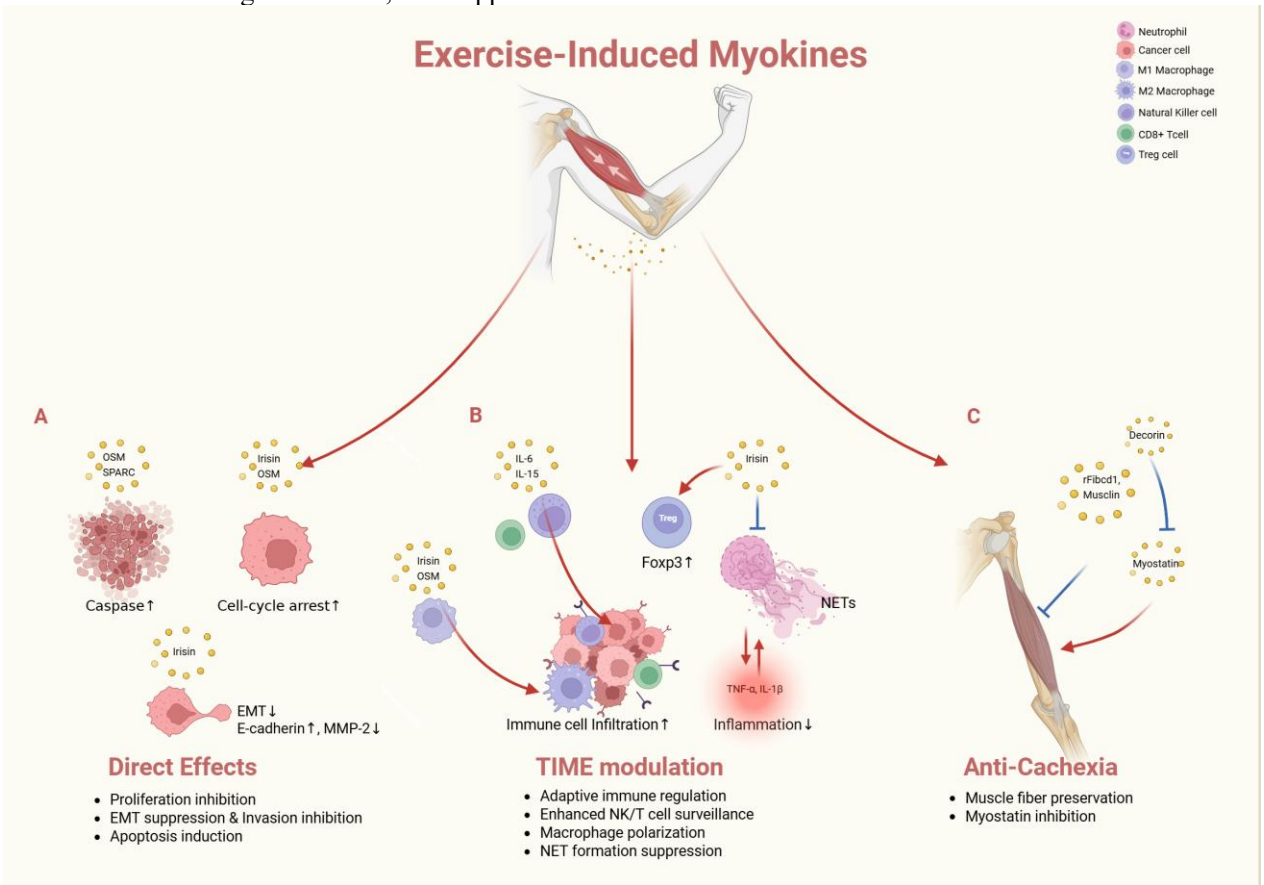

Figure 2. Myokine Network in Immunomodulation and Cancer Prevention. Exercise-induced myokines suppress tumorigenesis through a multi-faceted strategy that directly targets cancer cells and remodels the tumor immune microenvironment (TIME). **(A)** Direct Oncosuppression: Myokines including Irisin, OSM, and SPARC directly inhibit tumor cell proliferation, induce apoptosis, and suppress the epithelial-mesenchymal transition (EMT). **(B)** Immunomodulation: The network enhances both innate and adaptive

immunity. IL-6 and IL-15 boost NK cell surveillance, while Irisin and OSM promote anti-tumor macrophage polarization. Irisin also enhances Treg function and inhibits neutrophil extracellular trap (NET) formation. **(C)** Cachexia Attenuation: By maintaining systemic metabolic and muscular homeostasis, the myokine network helps counteract cancer-associated cachexia. *Icons were created with BioRender.com.* Abbreviations: NETs: neutrophil extracellular traps; EMT: epithelial-mesenchymal transition; TIME: tumor immune microenvironment; Treg: Regulatory T cell; NK cell: Natural Killer cell. ↓: inhibition; ↑: promotion.

7. The Muscle-Brain Axis

The muscle-brain axis represents the most sophisticated example of systemic myokine action, where all four cytoprotective programs—proteostasis, metabolic support, neuroinflammation resolution, and synaptic repair—converge to maintain cognitive function and counteract neurodegeneration [143].

7.1 Proteostasis

Neurodegeneration is fundamentally driven by a failure in proteostasis—the cellular system that maintains protein health. The accumulation of misfolded proteins like Aβ and tau in Alzheimer's disease (AD) and α-synuclein in Parkinson's disease (PD) is a hallmark of this age-related decline. The myokine network directly augments the brain's clearance mechanisms.

A key mechanism is the coordinated upregulation of BDNF. Beyond its well-established role in neuronal survival and synaptic plasticity, BDNF mechanistically reduces Aβ production by shifting amyloid precursor protein (APP) processing toward the non-amyloidogenic pathway, thereby reducing the generation of neurotoxic Aβ peptides [144, 145]. This BDNF-centric arm is powerfully reinforced by multiple myokines that elevate BDNF levels. For instance, irisin is known to elevate BDNF levels through the PGC-1α-FNDC5 pathway [146]. Similarly, apelin [147], insulin-like growth factor-1 (IGF-1) [148], and METRNL can cross the blood-brain barrier to upregulate BDNF expression, with METRNL additionally attenuating brain injury via inhibition of neuronal ferroptosis [123, 149]. The functional significance of this network is underscored by several human randomized controlled trials (RCTs) linking exercise-induced increases in BDNF to measurable improvements in cognitive performance [150].

Beyond Aβ, myokines enhance the clearance of other toxic aggregates. In PD models, BDNF inhibits the activity of endolysosomal cysteine proteases, which are abnormally activated and contribute to α-synuclein toxicity [151]. Additionally, myokines including LIF [152], FGF21, and apelin-13 [153] promote α-synuclein clearance through autophagy activation.

Collectively, the evidence demonstrates that multiple myokines converge on BDNF as a central node to regulate proteostasis. However, a critical challenge in translating this finding into therapies lies in elucidating how these signals are precisely and coordinately integrated, and whether they exhibit cell-type specificity. Clarifying these mechanisms will provide an indispensable theoretical foundation and precise targets for achieving the ultimate goal of developing exercise-mimicking therapeutics.

7.2 Neuroinflammation

Age-related dysregulation of brain immune cells is a critical driver of neurodegeneration. Spatiotemporal RNA-seq studies have revealed an accelerated aging phenotype in glial cells, identifying microglia as a primary contributor to brain aging [154]. The accumulation of locally senescent microglia is thought to drive brain-wide aging via the senescence-associated secretory phenotype (SASP), inducing paracrine senescence in neighboring cells, including other glial cells and neurons [155].

Within this context, myokines emerge as key modulators of microglial activity. Overactivated microglia contribute significantly to dopaminergic neuron death by releasing pro-inflammatory cytokines such as TNF-α and IL-1β[156]. Mechanistically, irisin suppresses this microglial-driven neuroinflammation by upregulating TFAM to support mitochondrial function [157] and by reinforcing the BDNF-TrkB signaling [158]. Similarly, BAIBA effectively reverses palmitate-induced hypothalamic inflammation and microglial activation [159].

Looking forward, research is expanding to target specific pro-aging inflammatory pathways within the brain. The cGAS-STING pathway has been directly implicated in age-related neuroinflammation and cognitive decline [160]. Intriguingly, a recent study on the muscle-kidney axis revealed that the myokine irisin inhibits cGAS-STING signaling [161], raising the compelling hypothesis that irisin, or other myokines, might employ a conserved strategy to quell this pathway within the brain. Validating this cross-organ mechanism will deepen our understanding of the muscle-brain axis and may hold promises for developing novel therapeutic strategies.

7.3 Cerebral Metabolism

The aging brain is characterized by a progressive energy crisis, manifesting as impaired glucose metabolism, mitochondrial dysfunction, and cerebral insulin resistance. This hypometabolic state, a hallmark of aging and neurodegenerative diseases, precedes clinical symptoms and establishes a vulnerable foundation for

pathology [162]. Within this context, the muscle-brain axis emerges as a pivotal endogenous system for brain energy rescue. Myokines, as mediators of exercise, translate peripheral metabolic improvements into direct central support, targeting multiple facets of the brain's energetic deficit.

Cerebral insulin resistance is a key pathophysiological feature of AD, disrupting crucial neuronal survival and plasticity pathways [163]. The muscle-brain axis counteracts this by translating peripheral metabolic improvements into central nervous system (CNS) benefits [164]. As detailed in Section 3, several myokines enhance peripheral insulin sensitivity. IL-6, for instance, has been shown to exert central effects by increasing hypothalamic GLP-1 and STAT3 signaling, thereby enhancing brain insulin responsiveness and energy homeostasis in murine models [165].

Concurrently, myokines are potent regulators of mitochondrial homeostasis. BDNF promotes mitochondrial biogenesis and facilitates the removal of damaged mitochondria via mitophagy in female mice [67, 166]. Similarly, irisin has been shown to reduce oxidative stress and neuronal apoptosis by inhibiting excessive mitochondrial fission and promoting mitochondrial biogenesis in PD models [167]. The myokine FGF21, whose serum levels correlate with mitophagy markers [168], is also implicated in maintaining mitochondrial homeostasis.

Notably, lactate has been redefined from a metabolic waste product to a crucial myokine with dual functions [169]. During exercise, it serves as a high-capacity energy substrate that the brain efficiently oxidizes, particularly under metabolic stress. Beyond its role as an energy substrate, lactate acts as a potent signaling molecule. Emerging evidence further positions lactate as a systemic epigenetic regulator, as intact lactate flux is necessary for exercise-induced reprogramming of the skeletal muscle methylome and transcriptome [170]. It directly stimulates the expression of genes pivotal for synaptic plasticity and cognitive function, including BDNF, c-Fos, and Zif268 [171, 172]. Crucially, studies in resting humans have demonstrated that intravenous lactate infusion alone is sufficient to trigger BDNF release in the brain, cementing its role as a direct neuroactive signal from muscle [173].

7.4 Synaptic Plasticity

Beyond clearing pathological insults and providing metabolic support, a fundamental mechanism by which myokines confer neuroprotection is through the direct enhancement of synaptic plasticity and the reinforcement of neural circuits. This action ensures that surviving neurons can maintain robust communication and adaptive function.

A key pathway is the exercise-induced upregulation of miR-17/20a-5p, which is delivered to the hippocampus via Mu-EVs. Upon delivery, this myokine-associated miRNA enhances synaptic plasticity and improves cognitive function by activating the mTOR signaling pathway [174]. This represents a direct, trans-organ mechanism through which muscle activity fine-tunes brain connectivity.

The repertoire of myokines regulating neural connectivity is expanding. Leukemia inhibitory factor (LIF), despite its transient signaling nature, promotes neuronal survival and protects against Aβ-induced neurotoxicity, potentially through stimulating c-fos in hippocampal cells [152]. Furthermore, prosaposin (PSAP) has been validated as a novel myokine with CNS-targeting effects in an Aβ-induced toxicity model [175]. The discovery of EV-delivered miRNAs and novel myokines like PSAP unveils a sophisticated communication system. A key future challenge is to determine how these distinct plasticity-promoting signals are integrated within neural circuits to produce a coherent cognitive outcome.

Collectively, these findings illustrate that the muscle-brain axis does not merely protect neurons from death but actively promotes the functional and structural resilience of neural networks. This positions muscle as a master regulator of cognitive resilience, integrating metabolic, anti-inflammatory, and pro-plasticity signals into a coherent anti-aging endocrine command.

8. Integrated Regulatory Mechanisms of the Myokine Network

The preceding sections have detailed how individual myokines counteract aging within specific organ systems. However, the true therapeutic potential of the myokine system lies in its capacity for trans-systemic coordination, where a single adaptation in one tissue initiates a cascade of benefits across multiple others. This integrated network effect, rather than isolated actions, underpins the systemic anti-aging potential of exercise. For example, the improvement in systemic glucose metabolism by myokines like irisin and IL-6 (as detailed in Section 3.1) reduces the accumulation of advanced glycation end-products (AGEs), thereby alleviating diabetes-associated bone abnormalities [176].

This trans-systemic coordination finds its molecular basis in the remarkable convergence of diverse myokines onto a limited set of evolutionarily conserved signaling hubs. The following sections will dissect how this convergence on pathways such as AMPK/NF-κB, Akt, PPARs, and epigenetic regulators forms the backbone of the myokine network, enabling a coordinated, multi-systemic defense against aging.

8.1 AMPK and NF-κB Pathways: Balancing Energy Metabolism and Inflammation

The aging-driven dysregulation of energy metabolism and the emergence of chronic low-grade inflammation are intimately linked, sharing common underpinnings largely governed by the opposing actions of AMPK and NF-κB [177]. The myokine network directly targets this dysregulated axis to counteract age-related metabolic and inflammatory decline.

On the metabolic front, the activation of AMPK signaling is a recurrent theme for myokine action [178]. For instance, FGF21 activates AMPK signaling to orchestrate systemic glucose and lipid metabolism [179]. This strategy is employed by a network of myokines, including Irisin, BAIBA, SPARC, and IL-15, which activate AMPK in metabolic tissues to enhance glucose uptake and fatty acid oxidation. The reliance on AMPK stimulation across various tissues underlies broad cytoprotective effects, including the amelioration of mitochondrial dysfunction, inflammation, and oxidative stress [180]. Beyond acute metabolic roles, the AMPK axis also mediates long-term adaptive programming. The administration of apelin activates AMPK in fetal muscle, conferring lasting protection against diet-induced obesity and establishing the apelin-AMPK axis as a key mediator of long-term metabolic health [181].

Concurrently, the myokine network directly suppresses the inflammatory arm of this circuit by inhibiting NF-κB signaling. This anti-inflammatory strategy is a common mechanism shared by several myokines. For instance, METRNL dose-dependently inhibits palmitate-induced NF-κB nuclear translocation, IκBα phosphorylation, and pro-inflammatory cytokine expression [57]. Likewise, irisin treatment attenuates LPS-induced TLR4/MyD88 activation, subsequently reducing downstream NF-κB signaling [182].

Through this coordinated regulation of both AMPK and NF-κB, the myokine network does not merely target individual diseases but addresses the fundamental, interconnected pathologies of metabolic decline and chronic inflammation. The convergence of multiple, structurally distinct myokines on this core antagonistic signaling axis provides compelling mechanistic evidence for the existence of a coordinated, endocrine-like network emanating from muscle. This dual targeting positions skeletal muscle as a master regulator of systemic health, translating the contractile cue of exercise into a coherent anti-aging endocrine signal.

8.2 Akt Pathway: Cell Survival and Organ Protection

The Akt (protein kinase B) signaling pathway is established as a central integrator within the myokine network, translating diverse extracellular cues into coordinated anti-aging responses. It functions as a master regulator, synchronizing metabolic homeostasis, anabolic processes, and cell survival programs across multiple tissues.

A key upstream axis activating Akt involves myokine-mediated receptor engagement. For instance, the newly identified myokine feimin binds to its receptor MERTK, directly initiating PI3K/Akt signaling to enhance glucose uptake and suppress hepatic glucose production [183]. Similarly, FNDC1 promotes muscle regeneration by activating integrin α5β1 and the downstream FAK/PI3K/AKT/mTOR cascade [184]. This paradigm of receptor-mediated Akt activation is complemented by unconventional mechanisms, such as that of IF1, which increases extracellular ATP to indirectly stimulate Akt [152].

This signaling convergence enables Akt to orchestrate a multi-systemic defense. In metabolic regulation, myokines like feimin and CLCF1 critically depend on Akt to improve systemic glucose tolerance [183, 185]. In muscle anabolism, FNDC1 and LIF activate Akt to drive protein synthesis, myoblast differentiation, and regeneration, thereby countering sarcopenia [184, 186]. For cytoprotection in non-muscular tissues, Akt serves as a common effector: irisin employs it to restore podocyte autophagy in diabetic kidney disease [187] and to protect chondrocytes [101]; METRNL similarly utilizes Akt for chondroprotection [102]; and FSTL1 is induced by muscle Akt and subsequently activates the Akt-eNOS signaling axis in endothelial cells to promote cell survival and revascularization in response to ischemia [188].

In summary, the Akt pathway operates as a fundamental signaling nexus, enabling the myokine network to execute a unified, yet context-sensitive, defense against age-related functional decline across organ systems.

8.3 PPAR Pathway: A Pivotal Hub for Lipid Metabolic Reprogramming

Research has established PPAR signaling as a pivotal hub for lipid metabolic reprogramming [189], a process greatly mediated by myokines. A well-characterized mechanism is the canonical AMPK-PGC-1α axis, which serves as a master switch that coordinately activates multiple PPAR subtypes. Within this axis, AMPK activation induces rapid increases in fatty acid oxidation via phosphorylation and inhibition of acetyl-CoA carboxylase (ACC) [190]. Under sustained activation, it transcriptionally upregulates PGC-1α, which in turn co-activates PPARs.

This signaling cascade potently activates different PPAR subtypes to orchestrate lipid metabolism: it activates PPARδ, as demonstrated by irisin, to stimulate white adipose browning [191], and it concurrently activates PPARα, evidenced by METRNL and BAIBA, to enhance fatty acid oxidation [97, 192]. Beyond direct receptor activation, myokines also fine-tune the PPAR network through inhibitory strategies. For instance, Mu-EVs deliver miR-146a-5p to adipose tissue, where it suppresses adipogenesis by targeting the GDF5-PPARγ axis [193].

Importantly, myokine signaling to PPARδ is not monolithic, and its metabolic effects are context-dependent. For instance, BAIBA and METRNL also engage the AMPK-PPARδ axis to enhance insulin signaling and attenuate inflammation [56, 57], demonstrating the pathway's pleiotropy beyond lipid metabolism. Furthermore, under conditions of metabolic stress, BDNF activates a distinct CaMKK2-PPARδ axis independent of AMPK, upregulating fatty acid oxidation genes to support skeletal muscle metabolic reprogramming and mitochondrial remodeling [66].

8.4 Epigenetic Remodeling

Beyond mediating rapid signal transduction, the myokine network also regulates epigenetic mechanisms to provide durability to the systemic anti-aging benefits of exercise. Histone deacetylases (HDACs) and the related NAD^+-dependent deacetylases, Sirtuins (SIRTs), play pivotal roles in this process by modulating genome accessibility, thereby consolidating acute myokine signals into long-term gene expression programs.

The direct regulation of HDACs by myokines represents a crucial pathway for epigenetic programming. For instance, the myokine METRNL activates AMPK signaling, leading to the translocation and "sequestration" of Class IIa HDACs (such as HDAC4) from the nucleus to the cytoplasm. This process relieves the transcriptional repression imposed by HDAC4 on metabolism-related genes, thereby enhancing GLUT4 transport and mitochondrial function, and ultimately improving cardiac function post-heart failure [194]. Similarly, Irisin improves cardiac function and insulin sensitivity by suppressing HDAC4 pathways [195]. This demonstrates that myokines can directly manipulate epigenetic machinery via core signaling hubs to initiate lasting adaptive changes.

Furthermore, the myokine network deepens its epigenetic influence by interacting with the energy sensors, Sirtuins. The activity of SIRTs is dependent on NAD^+, making them ideal bridges connecting cellular energy status to gene expression. Multiple myokines, including irisin, METRNL, BAIBA, and FGF21, converge on the SIRT1-PGC-1α axis to promote mitochondrial biogenesis and oxidative metabolism across various tissues [157, 196]. Complementing the regulation of HDACs and Sirtuins, exercise-induced ROS have emerged as potent epigenetic modulators. ROS can directly oxidize DNA and RNA or affect the activity of epigenetic enzymes, thereby reshaping the epigenome. This ROS-epigenetics axis is fundamental to exercise-induced adaptations, including the regulation of mitochondrial quality control proteins and the reprogramming of myokine expression, which together counteract the degenerative epigenetic landscape of aging [40]. This epigenetic convergence provides a molecular basis for the long-term metabolic benefits conferred by the myokine network.

9. Sexual Dimorphism and Age Dependency in Myokine Action

A critical emerging theme across metabolic, musculoskeletal, and neurological systems is the profound influence of sex and age on myokine signaling efficacy and functional outcomes. Substantial heterogeneity exists in human myokine responses, with circulating irisin levels being generally higher in males—a difference potentially linked to sex-specific lactate metabolism [197] —whereas the osteoprotective effect of L-BAIBA is more pronounced in males, as detailed in Section 4.2 [94].Seminal work has highlighted that although myokine expression levels and skeletal muscle cellular composition are broadly similar between sexes, their signaling and cross-tissue regulatory effects exhibit significant sexual dimorphism, largely modulated by estradiol [198].

The synergistic crosstalk between BDNF and estrogen receptor alpha (ERα) constitutes a core sex-specific regulatory mechanism in females [199]. The functional importance of this E2/ERα-BDNF axis is demonstrated by the highly overlapping metabolic phenotypes observed in muscle-specific BDNF knockout (MBKO) and muscle-specific ERα knockout (MERKO) female mice [200, 201]. This axis is therefore pivotal in explaining the observed sexual dimorphism in the severity of conditions like osteoporosis and sarcopenia, where postmenopausal women experience more severe declines in muscle and bone mass compared to men, a disparity strongly associated with the decline in estrogen levels [202, 203]. In contrast, the inherently lower circulating estrogen levels in males underpin a reduced basal activity of this circuit [204].

Given this established link between estrogen and BDNF signaling, the observed sexual dimorphism in neuroprotection is unsurprising. Substantial epidemiological evidence indicates that women not only

constitute the majority of AD cases but also exhibit faster progression from mild cognitive impairment (MCI) to AD [205]. At a molecular level, BDNF expression is positively regulated by estrogen, and the marked decline in circulating BDNF levels in women post-menopause is closely implicated in this accelerated cognitive decline and worsening AD pathology [206].

This paradigm of hormone-dependent sexual dimorphism extends beyond BDNF to other myokines. Irisin's protective role appears more pronounced in the female brain, with its cerebrospinal fluid levels showing a stronger correlation with AD biomarkers and cognitive scores in women [207]. Preclinical models confirm this sex-specific effect, demonstrating that exogenous irisin administration specifically reduces tau hyperphosphorylation and alleviates neuroinflammation in the hippocampus of female mice [208]. Conversely, irisin seems more critical for male skeletal development, likely due to inherent differences in gene expression profiles that render male bone homeostasis more dependent on proper irisin regulation [209].

Aging independently dysregulates this network by decoupling myokine production from tissue responsiveness, a phenomenon well-illustrated by the BAIBA-MRGPRD axis. While aged muscle retains the capacity to produce BAIBA, the responsiveness of bone cells to this molecule is significantly diminished due to an age-related downregulation of its receptor, MRGPRD, in osteocytes[94], representing a fundamental mechanism of age-related endocrine resistance. This impaired signal transduction explains the attenuated skeletal benefits of exercise in advanced age. The therapeutic implications of this axis are further nuanced by sex. While its efficacy declines with age, L-BAIBA supplementation can effectively regulate osteoclastogenesis and bone remodeling in ovariectomized mice, presenting it as a novel therapeutic candidate for postmenopausal osteoporosis (PMOP) [95]. This highlights that therapeutic outcomes depend not only on myokine availability but also on the receptor landscape and the endocrine environment of target tissues, both of which undergo significant changes with age and sex.

In summary, the sexual dimorphism in hormonal milieu and the age-dependent dysregulation of receptor systems collectively determine the outcome of myokine signaling. These findings necessitate a sex-sensitive and age-conscious perspective in future research and clinical translation. However, aging itself is a highly heterogeneous process, and the existing evidence is fragmented across different age groups and disease populations, with most studies focusing on a specific cohort and a limited set of myokines [210]. This fragmented paradigm obscures the distinction between universal anti-aging mechanisms and context-dependent actions, underscoring the need for stratified, multi-myokine analytical approaches. Developing myokine-based diagnostics and therapies will require a precise understanding of how these fundamental biological variables shape the muscle-organ axis.

10. Conclusion

The recognition of skeletal muscle as a secretory organ has fundamentally reshaped our understanding of exercise-promoted healthy aging. Moving beyond the cataloguing of individual myokines, this review illustrates how skeletal muscle orchestrates multisystem crosstalk, translating physical activity into systemic anti-aging benefits through metabolic synchronization, inflammation resolution, and epigenetic reprogramming. The emerging role of myokines as clinical biomarkers for predicting organ function decline and mortality risk opens a new frontier in translational gerontology.

However, translating these mechanistic insights into therapies is fraught with challenges. The therapeutic application of myokines like irisin is hampered by its short plasma half-life and inconsistent behavior across human populations [211]. Furthermore, their context-dependent actions, exemplified by the paradoxical role of musclin in obesity and the dual nature of myostatin inhibition, present significant safety concerns. Compounding these issues, human evidence for most myokines remains largely correlative, with a scarcity of causal interventional studies [212]. This evidential gap is exacerbated by profound sex and age dependencies in myokine signaling, necessitating stratified analytical approaches rather than one-size-fits-all solutions.

Informed by these challenges, two complementary therapeutic paths are emerging. The first leverages endogenous induction via personalized exercise prescriptions, capitalizing on distinct myokine signatures elicited by different exercise modalities (summarized in Table 2). The second path involves the exogenous administration of myokines or their mimetics, a strategy that faces considerable pharmacological hurdles, such as poor stability, off-target effects, and an inability to replicate the synergistic actions of the native myokine network. Notably, research on MG53, a key cell membrane repair protein, provides compelling proof-of-concept for this second pathway. Studies demonstrate that sustained, physiological elevation of circulating MG53 enhances multi-organ regeneration without metabolic side effects, highlighting the therapeutic potential of harnessing myokines via extracellular action. The safety and efficacy of intravenous recombinant human MG53 (rhMG53) in large animal models further solidify the viability of myokine-related biologics [213].

Promising strategies to overcome these limitations are under development, including innovative delivery systems such as PEGylated particles for sustained release [214], and protein engineering approaches. For instance, the engineered albumin-binding domain (ABD)-conjugated Irisin (ABD-Irisin) fusion protein exhibits an extended half-life and enhanced therapeutic potency, representing an effective strategy to improve pharmacokinetics and anti-inflammatory efficacy [215]. A particularly promising delivery paradigm involves the use of Mu-EVs. Their inherent stability and tissue tropism make them ideal "exercise mimetics", as demonstrated by irisin-enriched EVs that delay VSMC senescence.

Therefore, future clinical translation must adopt a multi-layered strategy. For healthy populations, personalized exercise remains paramount. For patients unable to exercise, Mu-EV-based therapies offer the most promising avenue for replicating systemic exercise benefits, while optimized myokine mimetics may be reserved for specific targets.

In conclusion, fully harnessing the therapeutic potential of myokines requires a paradigm shift from a reductionist focus on single molecules towards an integrated, systems-level understanding of their network properties. The future of healthy aging interventions lies at the intersection of exercise physiology, precision medicine, and bioengineering, ultimately depending on our ability to decipher the complex language of muscle-organ crosstalk.

Competing interests

All authors declare that there is no conflict of interest

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Data Availability

No data was used for the research described in the article

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