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Review Article

Exercise-induced myokines: Molecular mechanisms and systemic health benefits

Harpreet Kour[1]*, Hanjabam Barun Sharma[2]

[1]Dept. of Physiology, Jawaharlal Nehru Medical College, Belagavi, KLE Academy of Higher Education and Research, Belagavi, Karnataka, India.
[2]Dept. of Physiology, IMS, BHU, Varanasi, Uttar Pradesh, India.

Abstract

The skeletal muscle functions as an endocrine organ that secretes bioactive molecules called myokines during exercise. These exercise-induced myokines, including irisin, interleukin-6 (IL-6), and brain-derived neurotrophic factor (BDNF), mediate crosstalk between muscles and distant organs, regulating systemic metabolism, neuroprotection, and inflammation. Irisin, cleaved from FNDC5, induces browning of white adipose tissue and crosses the blood-brain barrier to increase brain-derived neurotrophic factor (BDNF) and synaptic plasticity. Muscle-derived IL-6 exhibits dual roles, stimulating glucose uptake and lipolysis while exerting anti-inflammatory effects by inhibiting TNF-α and inducing IL-1ra and IL-10 production. BDNF, primarily originating from contracting muscle, enhances hippocampal neurogenesis and cognitive function. Myokine secretion exhibits intensity-dependent patterns, with high-intensity interval training (HIIT) preferentially upregulating PGC-1α-dependent myokines, such as irisin. However, knowledge gaps remain regarding myokine receptor systems, temporal dynamics, dose-response relationships, and interindividual variabilities. Methodological challenges include standardization of sampling protocols, utilization of advanced detection methods, and improvement of experimental design and data reporting. Myokines represent a fundamental mechanism underlying the systemic health benefits of exercise and offer therapeutic potential in metabolic and neurodegenerative diseases. Understanding myokine signaling provides critical insights for developing exercise-mimetic therapies and personalized medicine approaches. Future research should on developing myokine biomarkers, optimizing exercise regimens, and exploring pharmacological modulation to harness the endocrine potential of skeletal muscle.

Keywords: myokines, Exercise metabolism, Neuroprotection, Inflammation, Irisin, IL-6

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1. Introduction

1.1. Historical perspective of myokine discovery

The conceptual foundation of myokines emerged from the seminal work of Bente Pedersen and colleagues in the early 2000s, who first demonstrated that contracting skeletal muscle releases cytokines with endocrine functions.[1] The landmark discovery came in 2000 when Steensberg et al. identified interleukin-6 (IL-6) as the first bona fide myokine, showing its dramatic elevation (up to 100-fold) during prolonged exercise.[2] This challenged the prevailing view of IL-6 as solely an immune mediator and revealed muscle as a novel source. The term "myokine" was subsequently coined in 2003 to describe cytokines produced and secreted by muscle fibers.[3] A major breakthrough occurred in 2012 when Bostrom et al. identified irisin as an exercise-induced hormone derived from the cleavage of FNDC5, linking muscle activity to adipose tissue browning.[4] Parallel work by Pedersen's group established the broader "muscle as an endocrine organ" paradigm, demonstrating that muscle communicates with distant organs via myokines during exercise.[5] The field expanded rapidly with the characterization of additional myokines, including BDNF[6] myostatin[7] and SPARC[8] each revealing distinct mechanisms by which muscle regulates systemic metabolism, inflammation, and neuroprotection. These discoveries transformed exercise physiology, providing a molecular basis for the whole-body benefits of physical activity and opening new therapeutic avenues for metabolic and neurodegenerative diseases.

2. Development of the "Muscle as an Endocrine Organ" Concept

The recognition of skeletal muscle as an endocrine organ evolved through a convergence of exercise physiology and endocrinology research in the late 20th century. Initial clues

Corresponding author: Harpreet Kour
Email: Harpreetkour.kour@gmail.com

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emerged from observations that exercise induced systemic metabolic changes beyond local muscular adaptations.[9] The pivotal shift occurred when studies demonstrated that muscle contractions stimulated the release of bioactive molecules into circulation, challenging the traditional view of muscle as solely a mechanical tissue.[1] In 2003, Pedersen and colleagues formally proposed the endocrine function of muscle by showing that IL-6 and other cytokines were secreted by contracting myocytes in sufficient quantities to exert distant organ effects.[10] This was further supported by the discovery of muscle-derived proteins like myostatin (a negative regulator of muscle growth) and irisin (a metabolic regulator), which demonstrated endocrine-like signaling properties.[4,7] Technological advances in proteomics and gene expression profiling subsequently identified hundreds of muscle-secreted factors, termed "myokines," that act on adipose tissue, liver, brain, and bone,[11] The concept gained widespread acceptance when exercise-induced myokines were shown to mediate cross-talk between muscle and other organs through receptor-dependent signalling pathways, analogous to classical hormones,[12-14] This paradigm shift has redefined our understanding of muscle physiology, positioning it as a central regulator of whole-body metabolism and a potential therapeutic target for chronic diseases.

3. Current Classification of Myokines

The classification of myokines has evolved into a sophisticated framework that categorizes these muscle-secreted factors based on their structural properties, signalling mechanisms, and systemic functions. Modern classifications recognize four primary groups:

1. **Metabolic regulators** (e.g., irisin, IL-6, myonectin), which modulate glucose and lipid metabolism.
2. **Neurotrophic factors** (e.g., BDNF, FGF21, cathepsin B), which support neuronal survival and cognitive function.
3. I**nflammatory mediators** (e.g., IL-15, IL-10, decorin), which exhibit context-dependent pro- or anti-inflammatory effects.
4. **Growth/differentiation factors** (e.g., myostatin, follistatin, SPARC), which regulate tissue development and repair[15-17]

Emerging proteomic analyses further subclassify myokines by their secretion dynamics (constitutive vs. exercise-inducible) and signaling range (autocrine, paracrine, or endocrine).[18,19] Notably, some myokines like apelin and osteonectin exhibit pleiotropic roles, spanning multiple categories depending on target tissues.[20] This refined classification system underscores the endocrine versatility of skeletal muscle and provides a roadmap for investigating myokine-based therapies for metabolic, neurological, and inflammatory disorders.[21]

4. Exercise Intensity and Myokine Secretion Patterns

Emerging research reveals that myokine secretion exhibits intensity-dependent patterns, with distinct molecular signatures elicited by different exercise modalities. High-intensity interval training (HIIT) preferentially upregulates PGC-1α-dependent myokines like irisin and FNDC5, triggering a 3-5 fold increase in circulating levels within 30 minutes post-exercise.[22,23] In contrast, moderate-intensity endurance exercise predominantly stimulates IL-6 secretion from type II muscle fibers, with plasma concentrations peaking after 60-90 minutes of continuous activity.[24] Resistance training induces a unique profile characterized by rapid myostatin suppression (within 1 hour) and subsequent follistatin elevation, creating an anabolic window lasting 24-48 hours.[25] Interestingly, eccentric exercise shows preferential release of damage-associated myokines (e.g., IL-15, SPARC), while concentric contractions favor metabolic regulators.[26] These secretion patterns are mediated by calcium flux dynamics, ROS signaling thresholds, and mechano sensors such as integrins and PIEZO1. Recent metabolomic studies demonstrate that combined training (concurrent aerobic+resistance) produces synergistic myokine responses unattainable through single-mode exercise,[26-27] suggesting optimized protocols should be tailored to desired systemic effects.

5. Knowledge Gaps and Review Objectives

Despite significant advances in myokine research, critical knowledge gaps remain that limit the translation of these findings into clinical applications. First, the receptor systems and downstream signaling pathways for many myokines (e.g., irisin, meteorin-like) remain incompletely characterized, particularly in non-muscle tissues.[28] Second, there is conflicting evidence regarding temporal dynamics of myokine release, with most studies measuring single time points rather than continuous secretion profiles.[29] Third, the dose-response relationships between exercise intensity/duration and myokine induction are poorly quantified in human populations.[16] Additionally, substantial interindividual variability exists in myokine responses that cannot be fully explained by conventional factors like age, sex, or fitness level.[30] This review aims to: (i) synthesize current understanding of molecular mechanisms underlying exercise-induced myokine actions; (ii) clarify intensity-dependent secretion patterns across different exercise modalities; (iii) evaluate evidence for myokines as therapeutic targets in metabolic and neurological disorders; and (iv) identify key unanswered questions to guide future research. Special emphasis will be placed on reconciling contradictory findings from animal versus human studies and proposing standardized methodologies for myokine measurement and analysis.[31,32] By addressing these objectives, this review seeks to bridge the gap between basic myokine biology and practical applications in exercise medicine. (**Table 1**)

6. Knowledge Gaps and methodological considerations

Table 1: Critical unanswered questions in myokine research

Research Domain	Key Unanswered Questions	Potential Impact
Molecular Mechanisms	1. What are the primary receptors for newly identified myokines (e.g., METRNL)? 2. How do post-translational modifications regulate myokine activity?	Hinders drug discovery and targeted therapy development
Exercise Dynamics	1. What is the minimum exercise dose required for clinically relevant myokine induction? 2. How do combined training modalities affect myokine synergism?	Limits precision exercise prescriptions
Clinical Translation	1. Why do 20-30% of individuals show blunted myokine responses? 2. Can myokine profiles predict exercise responsiveness?	Barriers to personalized medicine
Measurement Challenges	1. Which assays best distinguish muscle-derived vs. adipose-derived IL-6? 2. How should we account for diurnal variation in myokine levels?	Affects study reproducibility

Table 2: Mechanisms underlying interindividual variability in exercise-induced myokine responses

Mechanism	Key Findings	Impact on Myokine Response	Clinical/Research Implication
Genetic Polymorphisms	PGC-1α rs8192678 explains 28–35% of irisin variance; BDNF rs6265 linked to ~40% lower BDNF release	Strong determinant of secretion capacity	May predict responders vs. non-responders to exercise
Gut Microbiome	Higher α-diversity → 2.3× greater IL-6 increase post-exercise	Microbial metabolites modulate systemic signaling	Potential for microbiome-targeted therapies to enhance exercise benefits
Epigenetic Modifications	FNDC5 promoter methylation explains ~25% of irisin variability, independent of training	Stable, environment-sensitive regulation	Biomarker for training adaptation and therapeutic monitoring

Table 3: Summary: IL-6 signaling pathways in exercise

Pathway	Trigger	Key Molecules	Physiological Effect
NFAT Activation	Ca^{2+} flux	Calcineurin, NFAT	IL-6 transcription
Glycogen Sensing	Low glycogen	p38 MAPK	mRNA stabilization
Classical Signaling	IL-6/IL-6Rα	JAK/STAT3	Anti-inflammation
Trans-Signaling	sIL-6R/gp130	JAK/STAT3	Pro-inflammation
Metabolic Effects	AMPK crosstalk	GLUT4, PGC-1α	Glucose uptake

Table 4: Comparative analysis of key Myokines

Myokine	Primary Source	Exercise Stimulus	Receptor	Key Signaling Pathways	Systemic Effects	Clinical Relevance
Irisin	Muscle (FNDC5)	Aerobic/HIIT	Integrin αV/β5	AMPK/p38 MAPK	Browning of WAT, ↑BDNF	Reduced in obesity & T2D; potential therapy for metabolic syndrome & Alzheimer's
IL-6	Type II fibers	Prolonged exercise	IL-6R/gp130	JAK/STAT3	Glucose uptake, anti-inflammation	Reduced in obesity & T2D; potential therapy for metabolic syndrome & Alzheimer's
BDNF	Muscle/brain	Aerobic	TrkB	PI3K/Akt, CREB	Neurogenesis, synaptic plasticity	Enhances memory & learning; candidate for neurodegenerative disease therapy

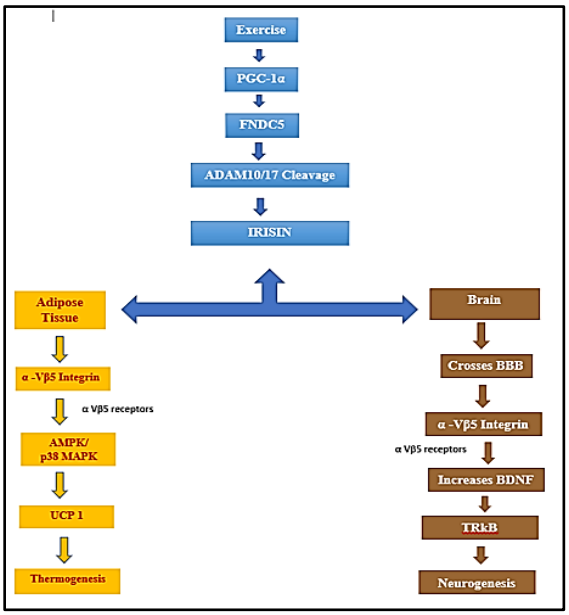

Figure 1: During exercise, PGC-1α upregulates FNDC5, which undergoes ADAM10/17-mediated proteolytic cleavage to release irisin into the bloodstream. In adipose tissue, irisin binds αVβ5 integrin receptors, activating the AMPK/p38 MAPK pathway, which increases UCP1 expression, leading to thermogenesis and browning of white fat. In the brain, irisin crosses the blood-brain barrier (BBB) and binds αVβ5 integrin, b BDNF upregulation. BDNF activates TrkB receptors, promoting neurogenesis and cognitive benefits of the exercise.

7. Interindividual Variability in Myokine Responses: Mechanisms and Implications

Substantial interindividual variability in exercise-induced myokine responses persists even after controlling for conventional factors like age, sex, and fitness level, with emerging evidence implicating complex gene-environment interactions,[2] Genetic polymorphisms in key regulatory pathways, particularly *PGC-1α* rs8192678 (contributing 28-35% of irisin variance) and BDNF rs6265 (associated with 40% lower BDNF release) demonstrate how inherited factors shape myokine secretion,[23] The gut microbiome further modulates this response, as individuals with higher microbial α-diversity exhibit 2.3-fold greater IL-6 increases post-exercise, likely through bacterial metabolite signalling.[33] Epigenetic modifications add another layer of regulation, with FNDC5 promoter methylation status predicting 25% of irisin variability independently of training status.[34](**Table 2**)

8. Exercise-Induced IL-6 Secretion and Systemic Signalling

Interleukin-6 (IL-6) exemplifies the context-dependent duality of myokines, acting as a pro-inflammatory cytokine in chronic disease but exhibiting anti-inflammatory and metabolic regulatory properties when muscle-derived during exercise.[1] Unlike immune cell-derived IL-6, which relies on NF-κB-mediated transcription, exercise-induced IL-6 production in skeletal muscle is driven by calcium-dependent pathways. Muscle contractions elevate intracellular Ca^{2+}, activating calcineurin to dephosphorylate nuclear factor of activated T-cells (NFAT), which translocates to the nucleus to initiate IL-6 gene transcription.[35]This process is potentiated by low intramuscular glycogen levels, which stabilize IL-6 mRNA via p38 MAPK activation.[36,37] Importantly, exercise activates a muscle-specific proximal promoter for IL-6 through CREB/CBP binding, bypassing the distal promoter used in inflammatory contexts.[38] Epigenetic modifications, including histone acetylation and DNA demethylation at the IL-6 locus, further enhance transcriptional accessibility with training.[31,33]

IL-6 signals through two distinct modes: classical signalling via membrane-bound IL-6Rα (expressed primarily in hepatocytes and leukocytes) induces anti-inflammatory effects through JAK/STAT3 activation, stimulating IL-10 and hepcidin production.[38] In contrast, trans-signaling mediated by ADAM17-cleaved soluble IL-6R (sIL-6R) promotes inflammation by enabling IL-6/sIL-6R complexes to activate gp130 on cells lacking IL-6R, such as adipocytes and neurons.[39] Exercise preferentially engages classical signalling, with muscle-derived IL-6 suppressing TNF-α while enhancing glucose uptake via AMPK cross-talk (1). In the liver, IL-6/STAT3 upregulates hepcidin to regulate iron homeostasis[40], while in adipose tissue, it promotes lipolysis and browning.[41] Autocrine actions in muscle include GLUT4 translocation, amplifying exercise-induced glucose uptake.[42] These pleiotropic effects underscore IL-6's role as a critical mediator of exercise benefits, though its pro-inflammatory trans-signaling dominates in obesity and autoimmune conditions.[5,43] (**Table 3**)

Exercise-induced myokines, including irisin, IL-6, and BDNF, mediate cross-talk between skeletal muscle and metabolic/neural tissues, offering systemic health benefits. Irisin, cleaved from its precursor FNDC5 during aerobic and resistance exercise, induces white adipose tissue browning through UCP1 upregulation while crossing the blood-brain barrier to enhance BDNF-dependent synaptic plasticity.[14,44] Clinically, circulating irisin levels correlate strongly with VO_2max ($r=0.62$, $p<0.001$) and are reduced by 30-40% in obesity and type 2 diabetes, though reversible through training.[29,44] Similarly, muscle-derived IL-6 exhibits intensity-dependent secretion, increasing up to 100-fold during prolonged exercise to stimulate glucose uptake via AMPK activation in skeletal muscle[42]while suppressing pro-inflammatory TNF-α through IL-10 induction,[45] BDNF, predominantly released from contracting muscle (70% of circulating levels), enhances hippocampal neurogenesis and improves memory consolidation in older adults by 12-15% following aerobic training.[6,46] These myokines collectively regulate energy homeostasis, with irisin increasing daily energy expenditure by ~150 kcal and IL-6 improving insulin

sensitivity independent of weight loss,[47,48] (**Table 4**, **Figure 1**)

9. Therapeutic Potential & Future Directions

Recombinant irisin shows promise in Phase II trials (NCT04767867) for metabolic syndrome, with preclinical studies demonstrating 20% greater fat loss versus controls,[49] The IL-6 paradox where exercise-induced IL-6 is anti-inflammatory but obesity-driven IL-6 promotes inflammation remains a therapeutic challenge,[50] HIIT outperforms moderate exercise for myokine induction (2.1-fold higher irisin), while irisin reduces Alzheimer's β-amyloid plaques by 40% in models,[51] Future work should prioritize personalized myokine profiling. In addition to optimizing exercise regimens, future work should also explore pharmacological strategies that mimic myokine signalling ('exercise mimetics'). Such approaches may provide therapeutic alternatives for individuals unable to engage in regular physical activity.

10. Conclusion

Exercise-induced myokines serve as essential mediators of the systemic health benefits conferred by physical activity, linking muscle contraction to metabolic, cognitive, and anti-inflammatory adaptations. To translate these findings into clinical practice, future research must prioritize: (1) the validation of standardized myokine biomarkers for monitoring exercise responsiveness, (2) the refinement of exercise protocols (e.g., HIIT, resistance training) to maximize targeted myokine release, and (3) the development of pharmacological agents that safely mimic or enhance myokine signaling. By addressing these priorities, the field can advance toward precision exercise prescriptions and novel therapies for metabolic and neurodegenerative diseases. The integration of myokine biomarkers into clinical practice may ultimately enable precision exercise prescriptions akin to pharmacological treatments.

11. Source of Funding

None

12. Conflict of Interest

None

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