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RESEARCH ARTICLE

SKELETAL MUSCLE AS AN ENDOCRINE ORGAN: THE MYOKINOME, INTERORGAN CROSSTALK, AND PATHOPHYSIOLOGICAL IMPLICATIONS A COMPREHENSIVE REVIEW

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ABSTRACT

Background: Skeletal muscle is now firmly established as the largest secretory organ in the human body. Far from serving merely locomotor and metabolic fuel-consuming roles, contracting muscle elaborates a diverse repertoire of bioactive peptides, proteins, and metabolites—collectively termed myokines or, more broadly, exerkines—that regulate the function of virtually every major organ system. Understanding this secretome has transformed our conception of physical activity from a mechanical intervention to a bona fide endocrine stimulus.This review synthesizes current biochemical, molecular, and translational evidence regarding the identity, regulation, and systemic actions of skeletal muscle-derived secretory factors. We examine the intracellular signaling cascades—including AMPK, PGC-1α isoforms, CaMKII, and JAK/STAT3 pathways—that govern myokine transcription and release, and detail interorgan crosstalk axes spanning the muscle–liver, muscle–adipose, muscle–bone, muscle–brain, and muscle–immune interfaces. We further discuss how myokine dysregulation contributes to the pathogenesis of type 2 diabetes, non-alcoholic steatohepatitis, sarcopenia, Alzheimer's disease, and malignancy, and evaluate the emerging therapeutic landscape of myokine mimetics and exercise pharmacology.Themyokinome constitutes a biochemically coherent endocrine network that mechanistically links physical activity to systemic health outcomes. Decoding this network offers a rational foundation for exercise prescription as targeted endocrine therapy and for the development of myokine-based pharmacologics in cardiometabolic, neurodegenerative, and oncological disease.

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INTRODUCTION

The concept of exercise as medicine is no longer metaphorical. Epidemiological data spanning decades robustly associate physical activity with reduced incidence of cardiovascular disease, type 2 diabetes mellitus, several malignancies, Alzheimer's disease, depression, and all-cause mortality (1,2). Yet the biochemical mechanisms underlying these benefits remained poorly defined for much of the twentieth century, largely because skeletal muscle—constituting 30–40% of total body mass in lean adults—was conceptualized exclusively in terms of its contractile and glucose-disposing functions. This view underwent a fundamental revision beginning in the early 2000s, when Pedersen and colleagues demonstrated that contracting human muscle secretes interleukin-6 (IL-6) at concentrations disproportionate to any local inflammatory stimulus, establishing it as an exercise-derived hormone rather than merely an inflammatory cytokine (3). The subsequent coinage of the term myokine—a cytokine or peptide produced and released by skeletal muscle in response to contraction—catalyzed a broader recognition that muscle functions as a true secretory endocrine organ (4). The discovery of irisin in 2012, a PGC-1α-regulated peptide that induces thermogenic browning of white adipose tissue, further crystallized this concept for the broader scientific community (5). Today, proteomic and transcriptomic interrogation of the skeletal muscle secretome has identified over 600 putative secreted factors, including classical peptide hormones, cytokines, growth factors, and non-peptide metabolites now collectively referred to as exerkines (6,7). These signals coordinate an integrated endocrine network spanning virtually every organ system, providing a biochemical substrate for the systemic benefits of physical activity and, conversely, for the pathological consequences of sedentary behavior. This review provides a comprehensive and mechanistically detailed account of the skeletal muscle secretome, with particular emphasis on the regulatory biology of key myokines, the molecular architecture of interorgan crosstalk, and the

translational implications for disease prevention and therapy. We adopt the organizational principle that muscle endocrinology is most productively understood through the lens of specific signaling axes rather than as an inventory of individual secreted factors.

HISTORICAL DEVELOPMENT OF THE MYOKINE CONCEPT: The notion that exercising muscle releases circulating factors dates to 1961, when Goldstein proposed the existence of a humoral substance mediating the insulin-independent glucose uptake of active muscle—a concept he termed the 'work stimulus' (8). This idea lay largely dormant for three decades, constrained by the absence of sensitive detection tools and a dominant paradigm in which exercise physiology focused on substrate flux, cardiac output, and autonomic adaptation. The molecular era of myokine research effectively began with the characterization of the acute-phase IL-6 response to exercise. Initial reports in the mid-1990s noted plasma IL-6 elevations following marathon running that were indistinguishable from those seen in sepsis; because IL-6 had been characterized primarily as a pro-inflammatory cytokine, this was paradoxically interpreted as evidence of exercise-induced tissue damage (9). The critical conceptual shift came from arteriovenous balance studies, catheterized limb preparations, and isolated myotube experiments demonstrating that IL-6 was actively secreted by contracting, undamaged muscle fibers in the absence of any inflammatory infiltrate (3). This established that muscle could function as an endocrine gland in the classical sense: producing a hormone in response to a physiological stimulus, releasing it into the circulation, and eliciting distant target organ responses. The term myokine was formally introduced by Pedersen in 2003 (4), and the subsequent decade witnessed exponential growth in the field. The identification of irisin as a PGC-1α-dependent adipokine-like myokine with thermogenic and neuroprotective properties (5), and the recognition that myostatin—a TGF-β superfamily member long studied in the context of muscle hypertrophy—operates as a systemic atrophy signal with adipogenic and skeletal effects (10), broadened the scope of muscle endocrinology beyond immunometabolism. The introduction of the term exerkine by Safdar and Tarnopolsky in 2016 to encompass exercise-induced bioactive factors from all tissues (cardiac, hepatic, adipose, osseous) acknowledged the conceptual evolution from organ-centric to systems-level thinking (7).

THE SKELETAL MUSCLE SECRETOME: SCOPE AND CLASSIFICATION

Transcriptomic and Proteomic Landscape: Systematic characterization of the muscle secretome has been enabled by combined proteomics of muscle-conditioned media, transcriptomics of contracting myotubes, and in vivo plasma proteomics before and after exercise. The Human Protein Atlas and the ExerCise Induced Factors (ECIF) database together catalogue over 600 proteins with evidence of secretion from skeletal muscle, though stringent criteria (signal peptide, membrane topology, detection in conditioned media, and in vivo exercise-responsive plasma changes) reduce the high-confidence myokinome to approximately 100–150 factors (6,11). The biological significance of the full catalogue remains incompletely characterized; this review focuses on those with robust mechanistic and physiological evidence.

Classification by Secretory Mechanism: Myokines are released via several distinct secretory pathways, with important implications for regulation and kinetics:

Classical ER–Golgi pathway: Signal peptide-bearing proteins including IL-6, myostatin, IGF-1, apelin, and myonectin are processed through the conventional secretory apparatus, packaged in secretory vesicles, and released by exocytosis upon appropriate stimulus. This pathway is subject to the full complement of post-translational modifications including glycosylation, which critically modulates bioactivity (e.g., irisin glycosylation).

Unconventional secretion: Several myokines lack canonical signal peptides and are secreted via membrane blebbing, multivesicular body fusion, or autophagy-related mechanisms. FGF-2, IL-1β, and HMGB1 belong to this category. Their release is often associated with cellular stress, membrane perturbation, or intense contractile activity exceeding physiological thresholds.

Extracellular vesicles (EVs): Exercise dynamically reprograms the EV secretome of skeletal muscle, with exosomes (50–150 nm, arising from multivesicular body fusion) and microvesicles (100–1000 nm, generated by plasma membrane budding) carrying proteins, lipids, and non-coding RNAs—particularly microRNAs (miRNAs)—to distant tissues (12). Muscle-derived EVs transfer functional miR-1, miR-133a, miR-133b, and miR-206 (myomiRs) as well as metabolic enzymes to liver, adipose, and cardiac tissue, with functional consequences for gene expression in recipient cells.

Metabolite secretion: Small-molecule metabolites with hormonal properties constitute an expanding category of exercise signals. Lactate, β-aminoisobutyric acid (BAIBA), kynurenic acid, and succinate are produced in stoichiometrically substantial quantities by contracting muscle and act on cognate receptors in distant tissues, challenging the classical protein-centric view of endocrine signaling (13).

Fiber-Type Heterogeneity of the Secretome: The quantitative and qualitative composition of the myokine output varies with fiber-type distribution and contraction pattern, reflecting differences in transcriptional programs. Type I (slow-oxidative) fibers, rich in PGC-1α, are the principal source of irisin, myonectin, BDNF, and FGF21, particularly under sustained aerobic stimulation (14). Type II (fast-glycolytic) fibers contribute disproportionately to the acute IL-6 surge during high-intensity glycolytic exercise, consistent with the glycogen-depletion signal that drives IL-6 transcription. This fiber-type specificity has direct implications for exercise prescription: endurance and resistance modalities differ substantially in their myokine output profiles, and understanding this specificity is necessary for tailoring exercise as a therapeutic modality.

INTRACELLULAR SIGNALING AND TRANSCRIPTIONAL REGULATION OF MYOKINE PRODUCTION

The PGC-1α Axis: Master Regulator of the Exercise-Induced Secretome: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) occupies a central position in the transcriptional regulation of exercise-induced myokine secretion. PGC-1α is a transcriptional

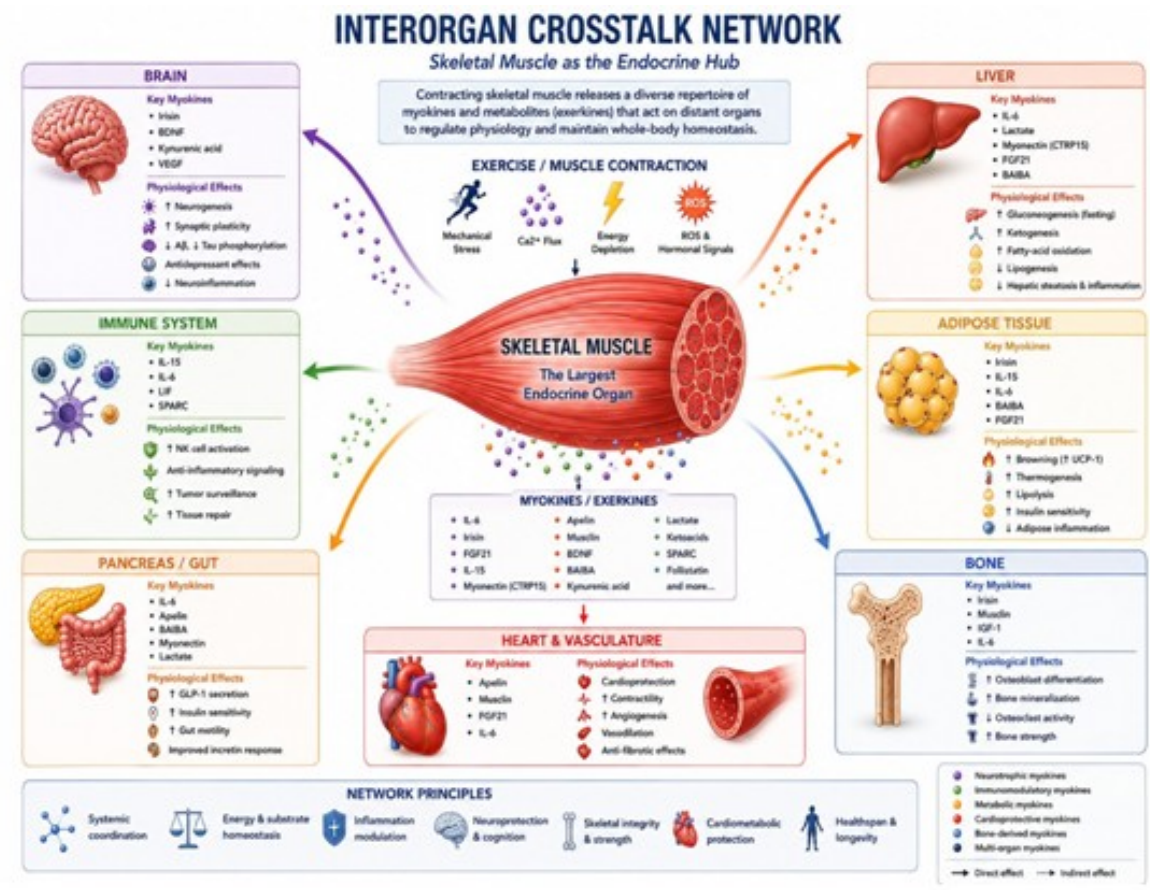

Fig. 1. Interorgan crosstalk network showing skeletal Muscle as the endocrine hub

co-activator rather than a direct DNA-binding factor; it amplifies the activity of PPARα, PPARγ, ERRα, NRF1, TFAM, and MEF2, thereby coordinating mitochondrial biogenesis, fatty acid oxidation, and myokine gene expression within a unified transcriptional program (15). AMPK (activated by the AMP:ATP ratio elevation of contracting muscle), CaMKII (activated by Ca^{2+} transients), and SIRT1 (activated by elevated NAD^{+}) converge on PGC-1α, increasing its expression via CREB and p38-MAPK-dependent mechanisms and its activity through SIRT1-mediated deacetylation. The transcriptional targets of PGC-1α relevant to the myokinome include FNDC5 (encoding the irisin precursor), FGF21, VEGF, and IL-15 (5,15).

Critically, PGC-1α exists as multiple splice isoforms with distinct exercise-type specificities. PGC-1α1 is the canonical isoform responsive to endurance exercise, whereas PGC-1α4—generated by an alternative promoter and splice site—is specifically induced by resistance exercise and drives anabolic signaling, including upregulation of IGF-1 and suppression of myostatin, through mechanisms distinct from the mitochondrial biogenesis program of PGC-1α1 (16). This isoform specificity provides a molecular basis for the well-recognized physiological differences between resistance and endurance exercise adaptations.

AMPK–mTORC1 Antagonism and Metabolic Sensing: AMPK and mTORC1 function as complementary energy-sensing switches whose antagonistic relationship governs the balance between catabolic and anabolic myokine programs. During energetic stress (AMP↑), AMPK is activated and phosphorylates TSC2 and Raptor, suppressing mTORC1 and shifting muscle metabolism toward oxidative substrate utilization and autophagy, while stimulating GLUT4 translocation and mitochondrial gene expression (17). In contrast, mTORC1—activated by IGF-1/PI3K/Akt signaling and amino acid sensing via Ragulator–RagGTPase complexes—drives protein synthesis and is the principal mediator of resistance exercise-induced hypertrophic signaling. The temporal dynamics of AMPK and mTORC1 activation during and after exercise determine the net myokine output profile.

Ca^{2+}-Dependent Pathways: CaMKII and Calcineurin/NFAT: Cytosolic Ca^{2+} transients generated by muscle excitation–contraction coupling activate two major downstream pathways with distinct transcriptional consequences. CaMKII phosphorylates and inactivates class IIa HDACs (HDAC4, 5, 7, 9), promoting their nuclear export and thereby derepressing MEF2-dependent genes including GLUT4 and various myokine transcripts. Calcineurin (protein phosphatase 2B), a Ca^{2+}/calmodulin-dependent phosphatase, dephosphorylates NFAT transcription factors, enabling their nuclear translocation and activation of Type I fiber phenotype genes including those encoding slow myosin heavy chains and oxidative enzymes (18). Both pathways are amplitude- and frequency-sensitive, providing a mechanism by which distinct exercise intensities and patterns generate quantitatively different myokine outputs.

NF-κB Signaling: Inflammation and the Acute Exercise Response: The canonical NF-κB pathway—activated by reactive oxygen species (ROS), mechanical stress, and

cytokine signaling through IκB kinase (IKK) complex—drives transcription of IL-6, IL-8, MCP-1, and other inflammatory myokines during intense exercise. Notably, exercise-generated ROS at moderate intensities activate antioxidant responses (Nrf2/ARE pathway) that ultimately suppress NF-κB—a molecular basis for the anti-inflammatory effects of regular moderate exercise (19). Sustained high-intensity exercise or exercise in the context of muscle damage produces prolonged NF-κB activation with pathological consequences. This dose-dependent, biphasic response of the NF-κB pathway underscores the importance of exercise intensity and recovery in determining the net inflammatory versus anti-inflammatory balance of the myokine output.

Epigenetic and Post-Transcriptional Mechanisms: A growing body of evidence indicates that exercise induces durable epigenetic remodeling of muscle gene regulatory regions. Acute exercise transiently reduces DNA methylation at CpG sites in the promoters of PGC-1α, GLUT4, and PDK4, facilitating their transcriptional activation; repeated exercise bouts lead to stable hypomethylation—a form of epigenetic 'exercise memory' that may underlie training adaptation (20). Histone modification dynamics, particularly histone H3 acetylation driven by HDAC nuclear export, amplify the transcriptional response to each exercise bout. At the post-transcriptional level, myomiRs (miR-1, miR-133a/b, miR-206, miR-499) regulate muscle gene expression by targeting key transcription factors (HDAC4, SRF, Sox6, myostatin 3'UTR) and are themselves regulated by exercise in a fiber-type- and intensity-dependent manner. Circulating myomiRs released in exosomes serve dual functions as biomarkers of exercise dose and as paracrine signals in recipient tissues—a paradigm shift in our understanding of non-cell-autonomous muscle signaling (12).

SELECTED MYOKINES: MECHANISMS AND SYSTEMIC ACTIONS

Interleukin-6: The Prototypical Exercise Myokine and Its Paradox: IL-6 remains the most extensively characterized myokine and illustrates the fundamental concept that muscle-derived cytokines operate in an endocrine mode qualitatively distinct from their inflammatory roles. During prolonged endurance exercise, plasma IL-6 concentrations rise 10- to 100-fold—magnitudes exceeding those observed in sepsis—and return to baseline within hours of exercise cessation (3). Crucially, this rise occurs in the absence of tissue damage markers (creatine kinase elevation, histological disruption, macrophage infiltration), establishing myocyte-intrinsic secretion as the source. The primary stimulus for exercise-induced IL-6 is intracellular glycogen depletion: glycogen phosphorylase activation decreases cytosolic glycogen content, which is sensed through a mechanism involving p38-MAPK and CREB-dependent IL-6 transcription. Ca^{2+}/NF-κB contributions are modulated by exercise intensity (3,9). The magnitude of the IL-6 response scales with exercise duration, intensity (%VO_2max), and total recruited muscle mass. Systemically, exercise-derived IL-6 acts on hepatocytes to transiently upregulate gluconeogenesis and enhance hepatic glucose output during sustained exercise; on adipocytes to stimulate lipolysis and fatty acid mobilization; and on intestinal L-cells to promote glucagon-like peptide-1 (GLP-1) secretion—an incretin effect with direct implications for insulin secretion and potentially for the metabolic benefits of exercise in T2DM (21). IL-6 also exerts anti-inflammatory effects in this context, suppressing TNF-α and IL-1β production and inducing IL-10 and IL-1Ra (4,19). The IL-6 paradox—wherein the same cytokine is pro-inflammatory in chronic disease (macrophage-derived, sustained) and anti-inflammatory in exercise (muscle-derived, transient)—is now understood to reflect differences in cellular source, concentration kinetics, receptor engagement context (cis- vs. trans-signaling), and downstream mediator profiles. This distinction has critical clinical implications: IL-6R antagonism (tocilizumab) in rheumatoid arthritis impairs exercise-induced GLP-1 secretion and metabolic benefits, illustrating the therapeutic complexity of targeting this axis (22).

Irisin (FNDC5): A Pleiotropic PGC-1α Effector: Irisin, a ~12 kDa glycoprotein generated by proteolytic cleavage of the type III fibronectin repeat-containing protein FNDC5, was identified by Boström *et al*. in 2012 as a PGC-1α-induced myokine mediating, at least in part, the beneficial effects of exercise on adipose tissue thermogenesis (5). FNDC5 transcription is driven by PGC-1α co-activation of ERRα; the FNDC5 protein undergoes proteolytic processing, and the ectodomain is shed as irisin. The identity and enzymatic basis of this cleavage remain incompletely defined, though ADAM proteases have been implicated (23). In white adipocytes, irisin binds αV integrin heterodimers, activating signaling cascades that upregulate UCP-1 expression, mitochondrial biogenesis, and fatty acid oxidation—the thermogenic browning or beiging program. This effect is phenotypically similar to cold exposure-induced browning, and consistent with the conceptual overlap between exercise and cold adaptation. In bone, irisin promotes osteoblast differentiation and suppresses osteoclastogenesis, providing a mechanistic basis for the well-documented positive effect of exercise on bone mineral density (24). The bone-anabolic effect of irisin is mediated in part through RANKL/OPG system modulation and Wnt pathway activation.

Particularly compelling evidence positions irisin as a mediator of exercise's neuroprotective and cognitive benefits. Irisin crosses the blood–brain barrier (unlike peripherally released BDNF, which does not), where it upregulates hippocampal BDNF expression, promotes neurogenesis, and reduces amyloid-beta (Aβ) accumulation and tau phosphorylation in Alzheimer's disease models (25). Circulating irisin levels are significantly reduced in Alzheimer's disease patients compared to cognitively intact controls, and intraventricular irisin administration reverses cognitive deficits in Alzheimer's mouse models (25). These findings position irisin as a candidate therapeutic agent and biomarker in neurodegeneration. Initial controversies regarding irisin's existence in humans, arising from antibody cross-reactivity concerns, have been largely resolved by mass spectrometry-based quantification demonstrating circulating human irisin at ~3–5 nM at rest, rising approximately 1.5- to 3-fold with acute exercise (23).

Myostatin (GDF-8): Endocrine Restraint of Muscle and Fat Mass: Myostatin (growth differentiation factor 8, GDF-8) is a member of the TGF-β superfamily constitutively produced and secreted by skeletal muscle that functions as an autocrine/paracrine and endocrine brake on muscle fiber size and satellite cell activity. Myostatin is synthesized as a prepropeptide, dimerized, and cleaved to yield a prodomain (latency-associated protein) that maintains the mature dimer in

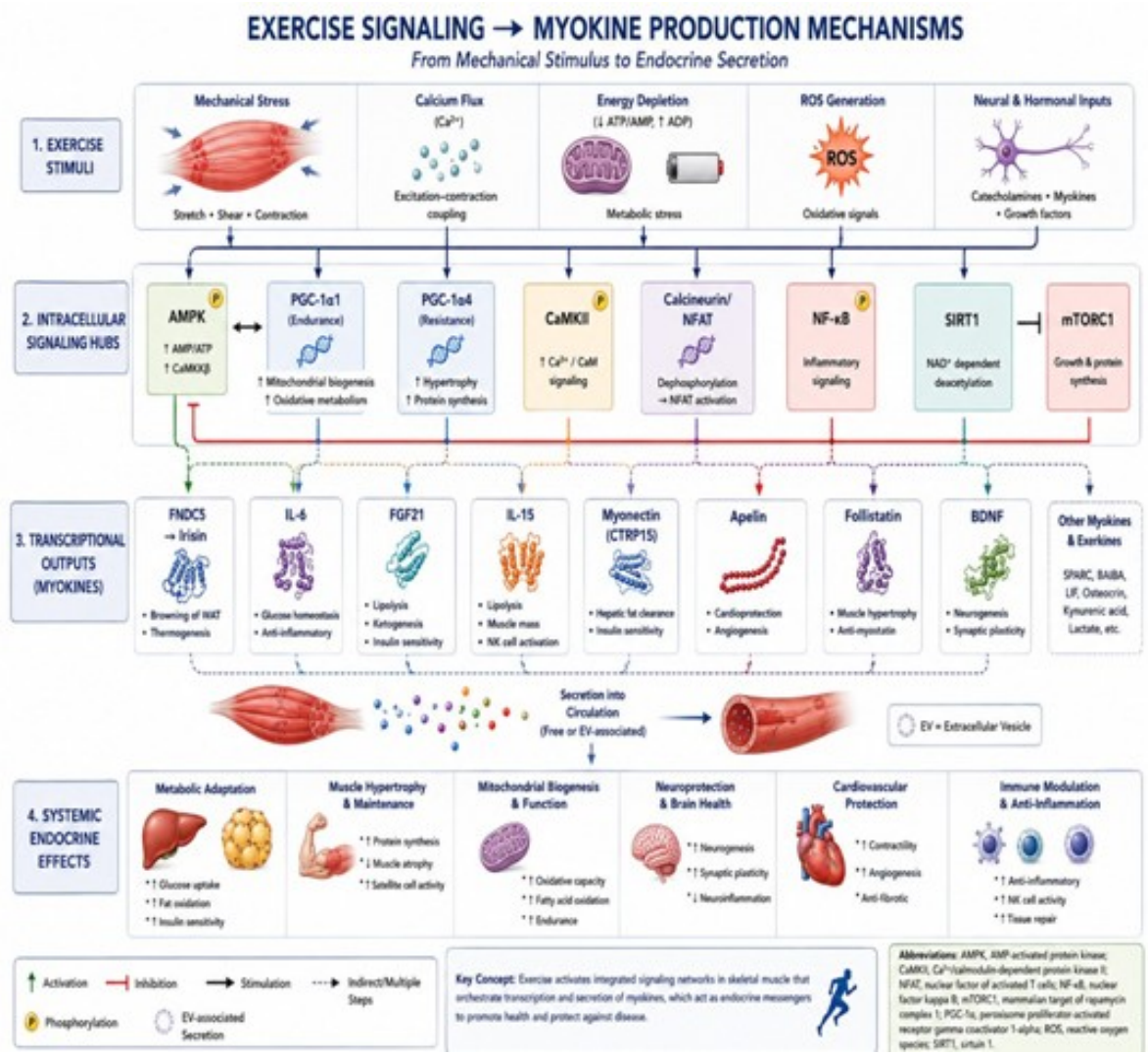

Fig. 2. Exercise signaling - myokine production mechanisms showing Mechanical Stimulus to Endocrine Secretion

Table 1. Representative myokines: sources, receptors, intracellular signaling, and primary systemic effects.

Myokine	Stimulus	Known Receptor / Pathway	Primary Systemic Actions
IL-6	Glycogen depletion, Ca^{2+}, NF-κB	IL-6R/gp130 → JAK/STAT3	↑Hepatic gluconeogenesis, adipose lipolysis, GLP-1 secretion; anti-inflammatory (acute)
Irisin (FNDC5)	PGC-1α (aerobic and resistance)	αV integrin → Akt/ERK	WAT browning, ↑bone formation, ↑hippocampal BDNF, ↓Aβ accumulation
Myostatin (GDF-8)	Constitutive; ↓by exercise	ActRIIB/ALK4-5 → SMAD2/3	↓Muscle hypertrophy, ↑adipogenesis, ↓osteogenesis, ↑atrophy E3 ligases
FGF21	PGC-1β, fasting, exercise	FGFR1c/KLB → ERK1/2	↑Lipolysis, WAT browning, ↑ketogenesis, ↑adiponectin
Myonectin (CTRP15)	Type I fibers, fed state	Unknown (C1q/TNF family)	↑Hepatic and adipose FA clearance; ↓plasma FFA
Musclin (Osteocrin)	Exercise	NPR-C (competitive)	↑cGMP via ANP/BNP signaling; ↑bone periosteal growth; cardioprotection
Apelin	Exercise, hypoxia	APJ receptor → Gi; NO↑	↑Cardiac contractility, vasodilation, ↑mitochondrial biogenesis, ↓aging phenotype
IL-15	Resistance exercise	IL-15Rα → JAK/STAT5	↓WAT mass, ↑NK cell proliferation, anabolic to muscle
SPARC	Contraction	Unknown	↑Apoptosis in colon epithelium; ↓adenoma formation; ↑bone collagen
Follistatin	Exercise (resistance)	Sequesters myostatin/activin	Endogenous myostatin antagonist; ↑net hypertrophic capacity
Meteorin-like (Metrnl)	PGC-1α4, exercise, cold	Unknown; eosinophil/IL-4 axis	WAT browning via eosinophil-driven IL-4; ↑insulin sensitivity
Lactate	Glycolysis; high-intensity	HCAR1 (GPR81); MCT transporters	↑Neuronal fuel, ↓adipose lipolysis (autocrine), cardiac substrate
BAIBA	Contraction; thymine catabolism	Unknown (adipocytes, osteocytes)	WAT browning, ↑hepatic FGF21, ↓obesity in animal models
Kynurenic acid	KAT activation (PGC-1α)	NMDA receptor antagonist (brain)	↓Neurotoxic kynurenine; antidepressant; neuroprotective

Table 2. Interorgan crosstalk mediated by skeletal muscle: key axes, mediators, and functional consequences

Axis (Direction)	Principal Myokine Mediators	Functional Consequence
Muscle → Liver	IL-6, lactate, alanine, myonectin, FGF21	↑Gluconeogenesis (acute), ↑FA clearance, ↑ketogenesis; ↓lipogenesis
Muscle → Adipose	IL-6, IL-15, irisin, FGF21, myonectin	↑Lipolysis, WAT browning/beiging, ↑FA clearance, ↓adipose mass
Muscle → Bone	Irisin, IGF-1, musclin, IL-6	↑Osteogenesis, ↓osteoclastogenesis, ↑bone mineral density
Muscle → Brain	Irisin, kynurenic acid, VEGF, IGF-1 (indirect)	↑BDNF, ↑neurogenesis, ↓Aβ, neuroprotection, antidepressant
Muscle → Pancreas (indirect)	IL-6 → gut L-cell GLP-1	↑Insulin secretion (incretin amplification)
Muscle → Heart	Apelin, musclin, FGF21	↑Contractility, cardioprotection, ↑ANP/BNP bioavailability
Muscle → Immune/Tumor	IL-6, IL-15, LIF, SPARC, EVs	↑NK/CTL activity, ↓colorectal adenoma, anti-inflammatory surge
Bone → Muscle (reciprocal)	Osteocalcin	↑Glucose uptake, ↑FAO, ↑IL-6, ↑exercise capacity
Adipose → Muscle (reciprocal)	Adiponectin (AdipoR1), leptin	↑AMPK/PGC-1α, ↑insulin sensitivity, ↑FAO capacity
Liver → Muscle (reciprocal)	IGF-1, FGF21, bile acids	↑Protein synthesis, ↑mitochondrial biogenesis, ↑FAO

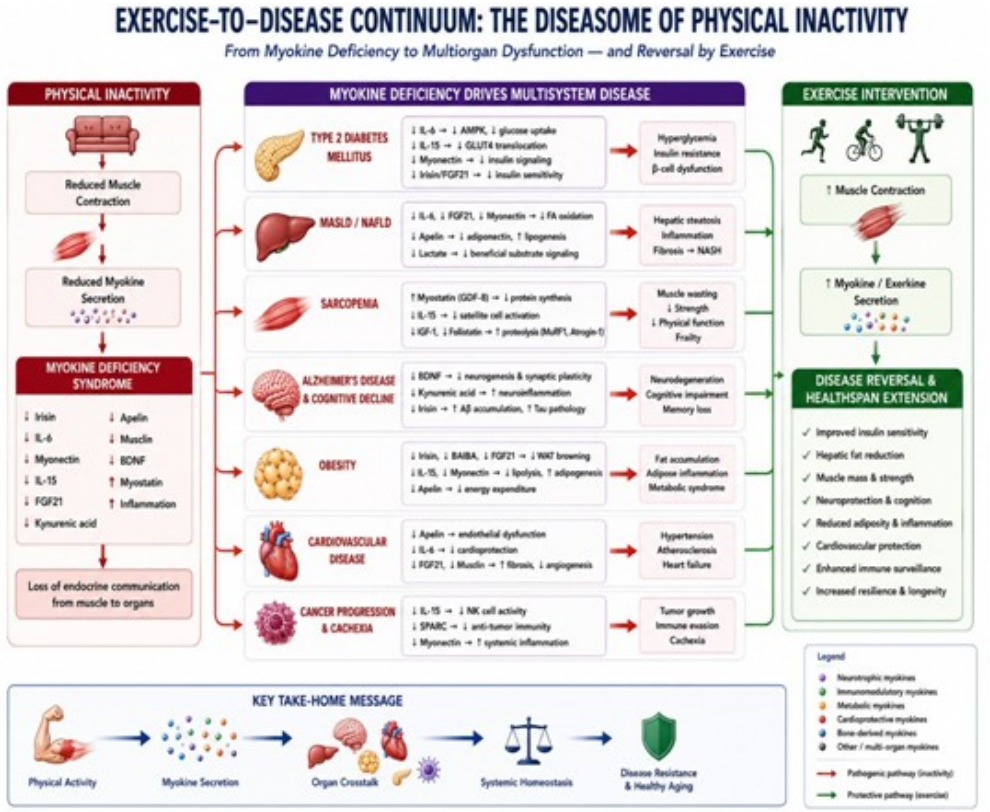

Fig:3. Exercise-to-disease continuum: the diseasome of physical inactivity

Table 3. Myokine dysregulation in major non-communicable diseases: mechanistic pathways and therapeutic targets

Disease	Predominant Myokine Perturbation	Key Pathogenic Mechanism	Therapeutic Opportunity
T2DM / Insulin Resistance	↓IL-6, ↓irisin, ↓myonectin, ↓GLUT4 response	↓GLP-1, ↓WAT insulin sensitization, ↓FA clearance	Exercise Rx; irisin analog; IL-6 modulation
MASLD / NASH	↓Myonectin, ↓FGF21 (early), ↑FGF21 resistance	↓Hepatic FA clearance; ectopic lipid; steatosis	Exercise Rx; FGF21 analogs (efruxifermin)
Sarcopenia	↑Myostatin, ↓follistatin, ↓irisin, ↓IGF-1, ↓LIF	↑Protein catabolism, ↓satellite cell activation, ↑myosteatosis	Anti-ActRIIB (bimagrumab); follistatin Rx
Alzheimer's Disease	↓Irisin (brain + plasma), ↓BDNF; ↓kynurenic acid	↑Aβ, ↑tau phosphorylation; ↑neurotoxic kynurenine	Irisin analogs; exercise protocol design
Colorectal Cancer	↓SPARC (sedentary), ↓IL-15	↓Apoptosis in adenoma cells; ↓NK surveillance	Exercise oncology; SPARC administration
Cancer Cachexia	↑Tumor activin A → ActRIIB; ↑myostatin in muscle	↑MuRF1/atrogin-1; ↓satellite cells; wasting	Bimagrumab; anti-myostatin mAb; exercise
Osteoporosis	↓Irisin, ↓musclin, ↓IGF-1	↓Osteoblast differentiation, ↑osteoclastogenesis	Irisin analogs; resistance exercise Rx
Depression	↓Kynurenic acid; ↓BDNF	↑Kynurenine (neurotoxic); ↓hippocampal neurogenesis	Exercise Rx; KAT supplementation strategies
Heart Failure	↓Apelin, ↓musclin, ↑myostatin	↓Contractility, ↓ANP/BNP benefit, ↑muscle wasting	Apelin analogs; supervised exercise Rx
Obesity	↓Irisin, ↓IL-15, ↓myonectin; ↑myostatin	↓WAT browning, ↑fat mass, sarcopenic obesity	Exercise Rx; irisin + GLP-1RA combination

Abbreviations:E3 lig., E3 ubiquitin ligase; ActRIIB, activin receptor IIB; FAO, fatty acid oxidation; MASLD, metabolic dysfunction-associated steatotic liver disease.

Table 4. Myokine-based therapeutic agents: mechanisms, development stage, and target conditions

Agent / Class	Target / Mechanism	Development Stage	Indication
Bimagrumab	Anti-ActRIIBmAb; blocks myostatin/activin	Phase II (completed; Ph III in progress)	Sarcopenia, T2DM-obesity, DMD
Landogrozumab / Trevogrumab	Anti-myostatin mAb	Phase II	Sarcopenia, muscular dystrophy
Efruxifermin (FGF21 Fc)	FGF21 analog; FGFR1c/KLB agonist	Phase II/III (MASLD/MASH)	MASLD, MASH (fibrosis regression)
Pegbelfermin	PEGylated FGF21	Phase II	MASLD, MASH
Recombinant irisin / FNDC5	αV integrin agonist; browning, neuroprotection	Preclinical / Phase I anticipated	Obesity, Alzheimer's, osteoporosis
Apelin / APJ agonists	APJ receptor (Gi); vasodilation, inotropy	Phase I/II	Heart failure, pulmonary hypertension
GDF-15 analogs (Ponsegromab)	GDF-15 neutralization (anti-cachexia)	Phase II	Cancer cachexia, heart failure
Exercise + GLP-1RA combination	Synergistic myokine + incretin axis	Clinical trial design phase	T2DM-obesity, sarcopenic obesity
KAT supplementation / exercise mimetics	↑Kynurenic acid; neuroprotection	Preclinical	Depression, Alzheimer's
EV-based cell-free therapy	Exercise-conditioned EVs as biologics	Preclinical	NAFLD, cardiac hypertrophy

Abbreviations: mAb, monoclonal antibody; Ph, Phase; RCT, randomized controlled trial; Rx, therapy; T2DM, type 2 diabetes mellitus.

a latent state; circulating myostatin is predominantly in the latent form, with activation occurring at target tissues via tolloid metalloproteinases (10). Myostatin binds activin receptor type IIB (ActRIIB) with high affinity, triggering sequential recruitment of ALK4/ALK5 (type I receptors) and phosphorylation of SMAD2 and SMAD3. Phospho-SMAD2/3 complexes with SMAD4 and translocate to the nucleus, where they suppress MyoD, myogenin, and Myf5 expression while upregulating atrophy-related ubiquitin ligases (MuRF1, atrogin-1) through FOXO transcription factor activation (10). The net result is inhibition of satellite cell proliferation, differentiation, and fusion, and promotion of protein catabolism. Genetic ablation of myostatin produces the hypermuscular phenotypes characterized in multiple mammalian species including cattle (Belgian Blue, Piedmontese), dogs (whippets), and one human child (10). Exercise suppresses myostatin expression, whereas immobilization, aging, cancer cachexia, and heart failure elevate it. The endogenous antagonists follistatin and follistatin-like 3 (FSTL3) sequester myostatin with high affinity; the follistatin:myostatin ratio is a critical determinant of the hypertrophic versus atrophic balance and is elevated by resistance training. Beyond muscle, myostatin acts on adipocytes to promote lipid accumulation, on osteoblasts to suppress bone formation, and on cardiac myocytes to regulate hypertrophic signaling—underscoring its role as a systemic tissue mass regulator rather than a purely muscle-autonomous factor (10).

Metabolite Myokines: Lactate, BAIBA, and Kynurenic Acid: The hormonal classification of metabolites produced at high flux during muscle contraction represents a conceptual expansion that parallels the historical recognition of steroids and thyroid hormones as signals derived from metabolic precursors. Lactate has been reconceptualized from an inert metabolic waste product to an intercellular signaling molecule and oxidative fuel. The lactate shuttle hypothesis (Brooks) recognizes that lactate produced by glycolytic fibers is a preferred oxidative substrate for cardiac muscle, slow-twitch muscle, and neurons (13). Lactate also signals through the G-protein coupled receptor HCAR1 (GPR81) expressed on adipocytes, where it acutely suppresses lipolysis during exercise to preserve circulating lipid concentrations—a potentially counter-intuitive autocrine feedback. HCAR1 expression in brain, testis, and retina implicates lactate as a broader signaling molecule. Plasma lactate concentrations rise 10- to 20-fold during high-intensity exercise.

β-Aminoisobutyric acid (BAIBA) is generated in contracting muscle from thymine catabolism (via the AGXT2 transaminase pathway) and valine catabolism (13). Circulating BAIBA induces thermogenic gene expression in white adipocytes (similar to irisin), promotes hepatic FGF21 production, and increases fatty acid β-oxidation. BAIBA also stimulates the release of RANKL decoy receptor in osteocytes, with potential bone-protective effects. In mouse models, BAIBA supplementation protects against diet-induced obesity and insulin resistance. Kynurenic acid is produced in exercising muscle through PGC-1α–driven induction of kynurenine aminotransferases (KATs), which convert kynurenine—a tryptophan catabolite elevated during inflammation and stress—to the neuroprotective metabolite kynurenic acid (26). Because kynurenine itself is neurotoxic and implicated in depression pathogenesis, the muscle-mediated peripheral conversion of kynurenine to kynurenic acid reduces its brain entry, providing a biochemically coherent mechanism for exercise's antidepressant and neuroprotective effects that is entirely independent of serotonin or BDNF changes.

INTERORGAN CROSSTALK: MUSCLE AS THE ENDOCRINE HUB

Muscle–Liver Axis: The muscle–liver crosstalk mediated by myokines represents a dynamic regulatory interface critical for hepatic metabolic homeostasis. Exercise-derived IL-6 acts on hepatocytes through gp130/STAT3 signaling to transiently promote gluconeogenesis (sustaining plasma glucose during sustained exercise) while suppressing hepatic lipogenesis—an effect that attenuates after exercise cessation as IL-6 levels decline (21). Lactate released from glycolytic muscle serves as a gluconeogenic substrate via the Cori cycle, providing a metabolic rather than hormonal link in this axis. Myonectin (CTRP15), a C1q/TNF-related protein enriched in oxidative muscle, is secreted postprandially and acts on liver and adipose to promote fatty acid uptake and storage, reducing circulating free fatty acid concentrations (27). This positions myonectin as a 'postprandial fuel-partitioning' myokine that coordinates lipid disposition following a mixed meal when muscle is adequately fueled.FGF21, although most highly expressed in liver, is also produced by muscle particularly during prolonged exercise with carbohydrate restriction. Muscle-derived FGF21 acts on adipose tissue to promote lipolysis, and on liver to upregulate ketogenesis—responses appropriate to the fuel demands of prolonged exercise. The FGF21–adiponectin–AMPK axis constitutes an important positive feedback loop in metabolic adaptation.

Muscle–Adipose Axis: The endocrine dialogue between muscle and adipose tissue is bidirectional and highly integrated. Muscle-derived myokines (IL-6, IL-15, irisin, FGF21) collectively promote lipolysis in white adipose tissue and stimulate the thermogenic browning program through distinct but converging mechanisms. IL-15, a type I cytokine upregulated by resistance exercise, selectively reduces white adipose mass while preserving or augmenting lean mass—a body composition effect of substantial clinical relevance (28).
In reciprocation, adipose-derived factors (adiponectin, leptin) regulate skeletal muscle insulin sensitivity and fatty acid oxidation capacity. Adiponectin, acting through AdipoR1 in muscle, activates AMPK and PGC-1α, thereby enhancing oxidative capacity and myokine secretion—a positive feedback loop that is disrupted in obesity where adiponectin levels are paradoxically reduced. This bidirectionality defines a muscle–adipose endocrine axis whose integrity is necessary for cardiometabolic health and is systematically disrupted in the metabolic syndrome.

Muscle–Bone Axis: Mechanical loading of bone through muscle contraction has long been recognized as a determinant of bone mineral density. The discovery that muscle also communicates with bone through humoral mediators—irisin, IGF-1, musclin, IL-6—establishes a biochemical dimension to muscle–bone functional coupling (24,29). Irisin acts on osteoblasts to promote differentiation and matrix mineralization, while musclin (osteocrin) suppresses osteoclastogenesis through competition with ANP/BNP at the clearance receptor NPR-C, thereby increasing bioavailable natriuretic peptides that enhance cGMP-mediated osteoblast function. The reciprocal signal from bone to muscle—osteocalcin, a bone matrix protein released during bone resorption—has emerged as a significant regulator of muscle metabolism during exercise. Osteocalcin acts through GPRC6A receptors on muscle to upregulate glucose uptake, fatty acid oxidation, and IL-6 expression, and stimulates the adrenal medulla to increase epinephrine, thereby integrating skeletal and energy metabolism during physical activity (30). This bone-to-muscle endocrine axis fundamentally reframes bone as an exercise-responsive endocrine organ, not merely a passive structural target.

Muscle–Brain Axis The relationship between exercise and cognitive function, long attributed to cerebrovascular effects and monoamine neurotransmitter changes, is now understood to involve direct myokine-mediated signaling to the brain. Multiple channels have been identified. First, irisin crosses the blood–brain barrier and upregulates BDNF expression in hippocampal neurons, promoting neurogenesis and synaptic plasticity—effects reversed by irisin neutralization in exercising mice (25). Second, the peripheral kynurenine-to-kynurenic acid conversion driven by muscle KAT activity reduces circulating neurotoxic kynurenine without directly affecting brain kynurenic acid (which is produced locally), effectively reducing tryptophan-derived neurotoxic metabolite availability (26). Third, exercise-induced VEGF and IGF-1 promote cerebrovascular angiogenesis and hippocampal neurogenesis through mechanisms that are partially myokine-mediated and partially hemodynamic. The translational significance of these findings is amplified by the observation, in a landmark 2020 study by Horowitz *et al*., that blood from young exercised mice, when transfused into aged sedentary animals, transferred cognitive benefits including ↑hippocampal neurogenesis and ↑spatial memory—effects attributable in part to circulating factors including irisin (31). This positions the exercise-induced secretome as a potentially 'youthful' paracrine signal with implications for the biology of aging.

Muscle–Immune Axis: The anti-inflammatory effects of regular moderate exercise are well documented epidemiologically, and myokines provide a plausible biochemical substrate. The acute IL-6 surge from exercise drives anti-inflammatory cytokine cascades (IL-10, IL-1Ra) and suppresses TNF-α; IL-15 expands NK cell populations and potentiates cytotoxic T lymphocyte function; LIF (leukemia inhibitory factor) promotes satellite cell activation while modulating macrophage polarization toward the M2 (tissue repair) phenotype (4,19).

SPARC (secreted protein acidic and rich in cysteine), upregulated in contracting muscle, has attracted particular interest for its anti-tumor immune properties in the colon: SPARC induces apoptosis in colorectal adenoma cells, provides a mechanistic basis for the consistently observed inverse association between physical activity and colorectal cancer incidence, and is suppressed in sedentary individuals (32). The muscle–immune axis thus extends beyond systemic inflammation suppression to encompass direct tumor immunosurveillance and anti-oncogenic mechanisms.

EXTRACELLULAR VESICLES AS MEDIATORS OF MUSCLE-DERIVED INTERORGAN COMMUNICATION: Extracellular vesicles (EVs) released by skeletal muscle constitute an underappreciated but mechanistically significant dimension of the muscle secretome. Exercise acutely increases total EV concentration in plasma, with muscle-derived EVs identifiable by surface markers including CD9, CD63, CD81 (tetraspanins), and the myosin heavy chain peptide content (12). EV cargo changes dynamically with exercise modality, intensity, and training state. The functional significance of muscle-derived EVs lies primarily in their miRNA payload. MyomiRs—miR-1, miR-133a, miR-133b, miR-206, and miR-499—are enriched in muscle-derived EVs and, upon uptake by recipient cells (hepatocytes, adipocytes, cardiomyocytes), alter gene expression in a physiologically relevant manner. miR-1 and miR-133 target cardiac hypertrophy regulators and metabolic genes; miR-206 promotes differentiation and is suppressed in amyotrophic lateral sclerosis, implicating its muscle-derived circulating form in neuromuscular cross-talk. miR-181 (miR-181a/b) is upregulated by aerobic exercise and targets SIRT1 regulators in liver and adipose, modulating insulin sensitivity (12). Protein cargo of exercise-induced EVs includes heat shock proteins (HSP70, HSP90α) with immunomodulatory properties, GAPDH, and fragments of metabolic enzymes. Lipid cargo includes ceramide species and sphingosine-1-phosphate that signal through cognate receptors on vascular and immune cells. The therapeutic exploitation of exercise-conditioned EVs as drug delivery vehicles or cell-free biologics is an active area of research, with proof-of-concept demonstrations in animal models of cardiac hypertrophy and NAFLD.

PATHOPHYSIOLOGICAL IMPLICATIONS: THE DISEASOME OF MYOKINE DEFICIENCY

Conceptual Framework: Pedersen introduced the concept of the 'diseasome of physical inactivity' to describe the cluster of non-communicable diseases that share, as a common

pathophysiological substrate, deficient myokine signaling consequent on habitual physical inactivity (33). This framework posits that myokine deficiency is not merely associated with disease but is causally involved in its pathogenesis—an assertion supported by mechanistic evidence from cell, animal, and human studies. In this framing, skeletal muscle hypofunctionality constitutes an endocrine deficiency state analogous to hypothyroidism or hypogonadism, with system-wide metabolic, inflammatory, and trophic consequences.

Type 2 Diabetes and Insulin Resistance: Physical inactivity reduces GLUT4 expression and AMPK activity in skeletal muscle, impairs exercise-induced GLUT4 translocation, and diminishes PGC-1α-driven metabolic reprogramming—resulting in a blunted myokine secretory response to any given bout of exercise. The consequent reduction in IL-6-driven GLP-1 secretion, irisin-mediated adipose insulin sensitization, and myonectin-facilitated hepatic lipid clearance creates a systemic environment permissive for progressive insulin resistance and dyslipidemia. Conversely, acute exercise in T2DM patients acutely and substantially improves glycemic control through both insulin-independent GLUT4 translocation and myokine-mediated interorgan effects (17).

Non-Alcoholic Steatohepatitis (MASLD): Skeletal muscle mass is inversely associated with hepatic steatosis severity independent of body mass index—an epidemiological observation now supported by mechanistic myokine data.
Reduced myonectin in sedentary individuals impairs hepatic fatty acid clearance; reduced FGF21 diminishes adipose lipolytic coordination; and reduced IL-6 blunts hepatic STAT3-driven lipid export. In mouse models, conditional PGC-1α deletion in muscle (mimicking physical inactivity) produces hepatic steatosis in the absence of dietary perturbation, reversible by administration of conditioned medium from exercised myotubes—demonstrating direct causality (34).

Fig:3. Exercise-to-disease continuum: the diseasome of physical inactivity: From Myokine Deficiency to Multiorgan Dysfunction - and Reversal by Exercise

Sarcopenia and Frailty: The myokinome of aging skeletal muscle is characterized by increased myostatin, reduced irisin, reduced IGF-1, reduced follistatin, and blunted exercise-induced IL-6 and LIF responses—collectively creating a pro-atrophic, pro-inflammatory, and pro-adipogenic milieu (35). This myokine profile is not merely epiphenomenal to the loss of muscle mass; it constitutes an active driver of sarcopenic pathology through: (1) impaired satellite cell activation (↓LIF, ↓IGF-1); (2) accelerated protein catabolism (↑myostatin → MuRF1/atrogin-1 upregulation); (3) fat infiltration of muscle (myosteatosis; ↑myostatin promotes lipogenesis in fibro-adipogenic precursors); and (4) systemic pro-inflammatory signaling contributing to inflammaging. Sarcopenia thus functions as an endocrine disorder, not merely a structural one.

Alzheimer's Disease and Neurodegeneration: Epidemiological evidence linking physical inactivity to Alzheimer's disease risk is compelling, with a hazard ratio reduction of approximately 30–45% associated with regular exercise in longitudinal cohorts (1). Mechanistic studies identify multiple myokine-mediated pathways: irisin deficiency in Alzheimer's brain is well-documented; irisin supplementation in transgenic Alzheimer's mice reduces Aβ plaque burden, reduces tau hyperphosphorylation, and improves spatial memory performance (25). The kynurenine-to-kynurenic acid shunting mechanism provides an additional neuroprotective axis. Furthermore, exercise-induced lactate is a preferred fuel of hippocampal neurons during cognitive tasks and enhances long-term potentiation through HCAR1-independent mechanisms involving NMDA receptor modulation.

Cancer: The Muscle–Tumor Axis: The anti-tumor properties of exercise-induced myokines operate through multiple complementary mechanisms. SPARC directly induces apoptosis in colorectal adenoma and carcinoma cells in vitro and reduces polyp number in APC-mutant mouse models; its circulating levels are significantly lower in sedentary than in physically active individuals (32). IL-15 expands and activates NK cell and cytotoxic T lymphocyte populations capable of tumor immunosurveillance, while exercise-derived IL-6 exerts context-dependent anti-tumor effects through immune modulation. Conversely, the muscle–tumor axis is exploited pathologically in cancer cachexia. Tumor-derived activin A, myostatin, and GDF-15 activate ActRIIB on muscle, driving SMAD2/3-mediated transcription of atrophy programs (MuRF1, atrogin-1, fbxo32) and suppressing satellite cell activation, resulting in progressive muscle wasting that is the direct cause of death in approximately 20–30% of cancer patients (36). Anti-ActRIIB therapy (bimagrumab) and anti-myostatin antibodies are being evaluated in randomized trials for cancer cachexia with promising preliminary results.

Table 3. Myokine dysregulation in major non-communicable diseases: mechanistic pathways and therapeutic targets

Abbreviations:E3 lig., E3 ubiquitin ligase; ActRIIB, activin receptor IIB; FAO, fatty acid oxidation; MASLD, metabolic dysfunction-associated steatotic liver disease.

THERAPEUTIC IMPLICATIONS: EXERCISE AS ENDOCRINE THERAPY AND MYOKINE PHARMACOLOGY

Exercise Prescription as Endocrine Therapy: The myokine paradigm reframes exercise prescription in mechanistic endocrinological terms: prescribing exercise is prescribing a myokine secretagogue regimen whose output depends on modality, intensity, volume, and the patient's fiber-type composition. Endurance exercise preferentially activates the IL-6/irisin/FGF21 axis through PGC-1α1, making it the preferred modality for interorgan metabolic crosstalk, adipose browning, and neuroprotection. Resistance exercise preferentially activates the PGC-1α4/IGF-1/follistatin axis and mTORC1-mediated protein synthesis, making it the preferred anti-sarcopenic modality. A dose–response relationship exists for most myokines, with greater exercise duration, intensity (% VO_2max), and recruited muscle mass producing proportionally larger acute secretory responses. Training adaptation shifts baseline myokine profiles chronically: trained individuals exhibit higher resting irisin, lower resting myostatin, higher follistatin:myostatin ratios, greater acute IL-6 responsiveness per unit workload, and enhanced EV myomiR secretion. These adaptations represent the mechanistic basis for the training-specific health benefits that accrue over months and years of regular exercise.

Myokine Mimetics and Novel Biologics: The identification of specific myokines as mechanistically essential for exercise benefits has catalyzed interest in pharmacological mimicry. Several agents are in advanced development:

Irisin analogs: Recombinant human irisin and FNDC5 ectodomain fragments demonstrate adipose browning, neuroprotection (↓Aβ, ↑BDNF), and bone anabolic effects in animal models at circulating concentrations achievable with pharmacological dosing. Phase I trials are anticipated. A critical limitation is the short circulating half-life of native irisin, necessitating PEGylation or other stability-engineering strategies.

Anti-myostatin/anti-ActRIIB biologics: Bimagrumab (anti-ActRIIB monoclonal antibody), landogrozumab (anti-myostatin), and trevogrumab have been tested in randomized controlled trials for inclusion body myositis, Duchenne muscular dystrophy, sarcopenia, and obesity. Bimagrumab notably demonstrated significant lean mass gain and fat mass reduction in a Phase II trial in T2DM patients with obesity, suggesting dual efficacy in sarcopenic obesity (37).

FGF21 analogs: Efruxifermin (FGF21 Fc fusion protein) and pegbelfermin have demonstrated efficacy in reducing hepatic steatosis and fibrosis in Phase II/III trials for MASLD/MASH, representing the first class of agents to show histological improvement including fibrosis regression in late-stage disease (38).

Apelin analogs: Apelin receptor (APJ) agonists are in early development for heart failure and pulmonary arterial hypertension, exploiting the cardiotonic and vasodilatory properties of this exercise-induced myokine.

The GLP-1 Connection and Synergy with GLP-1 Receptor Agonists: A mechanistically important interaction exists between the muscle endocrine system and GLP-1 pharmacology. Exercise-derived IL-6 directly stimulates GLP-1 secretion from intestinal L-cells—an effect demonstrable by IL-6R blockade abolishing a portion of the post-exercise incretin response (21). This identifies muscle-derived IL-6 as an endogenous GLP-1 secretagogue, suggesting that the combination of exercise and GLP-1 receptor agonists (semaglutide, liraglutide, tirzepatide) may produce supra-additive metabolic benefits through convergent and partially non-overlapping pathways. Conversely, GLP-1 receptor agonists—through their weight-reducing and anti-inflammatory effects—may restore myokine secretory capacity in obese and sarcopenic patients, creating a virtuous cycle. Early clinical data suggest that exercise combined with GLP-1RA therapy better preserves lean mass than GLP-1RA alone, consistent with the hypothesis that exercise-induced myokines attenuate the lean mass reduction associated with GLP-1RA-driven caloric restriction.

Precision Exercise Medicine: Individual variability in myokine responses to exercise is substantial and determined by genetic factors (PGC-1α promoter polymorphisms, FNDC5 Arg/Cys variant at position 32 affecting irisin processing), fiber-type composition (ACTN3 R577X genotype), sex (irisin exhibits sexually dimorphic expression), age (progressive myokine blunting), and metabolic state (insulin resistance reduces exercise-induced GLUT4 translocation and PGC-1α activation). As plasma proteomic platforms make large-scale myokine profiling clinically accessible, precision exercise prescription guided by individual myokine secretory phenotypes becomes a tractable goal. The integration of exercise physiology, metabolomics, and genomics defines the emerging field of exercise omics (7).

Table 4. Myokine-based therapeutic agents: mechanisms, development stage, and target conditions.

Abbreviations: mAb, monoclonal antibody; Ph, Phase; RCT, randomized controlled trial; Rx, therapy; T2DM, type 2 diabetes mellitus.

CURRENT GAPS AND FUTURE RESEARCH DIRECTIONS

Despite remarkable progress, several fundamental questions remain unresolved and constitute the frontier of muscle endocrinology:

Myokine receptor biology: For a substantial proportion of identified myokines—including myonectin, musclin, and BAIBA—cognate receptors remain unknown, precluding precise mechanistic delineation and rational drug target identification. Systematic deorphanization using proximity labeling proteomics and CRISPR-based screens is a priority.

Physiological concentrations and bioavailability: Many myokine studies employ supraphysiological concentrations in cell culture experiments, raising questions about physiological relevance. The development of standardized, mass spectrometry-validated assays for circulating myokines—accounting for diurnal variation, fasting state, and matrix effects—is essential for reliable clinical translation.

Sex and age as biological variables: The myokinome is sexually dimorphic and age-dependent, yet many foundational studies were conducted in young male subjects. Sex- and age-stratified mechanistic studies are required to develop appropriate exercise and pharmacological interventions for women, older adults, and adolescents.

Dose–response and temporal dynamics: The kinetics of myokine secretion, receptor occupancy, downstream signaling, and target organ response are incompletely characterized for most factors. Mathematical modeling integrating PK/PD principles with muscle physiology may enable optimized exercise prescription protocols and pharmacological dosing regimens.

EV biology and cargo validation. While the exercise-induced EV secretome is increasingly catalogued, the functional significance of individual EV-cargo components in vivo—particularly miRNAs whose concentrations in EVs may be below stoichiometrically relevant thresholds for target mRNA repression—requires rigorous validation.

Integration with gut microbiome. Exercise-induced changes in gut microbiome composition produce metabolites (short-chain fatty acids, bile acid species, urolithins) with myokine-like properties, and the microbiome modulates the systemic inflammatory environment that determines myokine receptor sensitivity. The exercise–gut microbiome–myokine axis is poorly characterized but likely significant.

CONCLUSIONS

The recognition of skeletal muscle as a major endocrine organ constitutes one of the most significant conceptual advances in physiology and metabolic medicine of the past three decades. The myokinome—comprising peptide hormones, cytokines, growth factors, and bioactive metabolites elaborated by contracting muscle—coordinates an integrated interorgan communication network whose disruption underlies the pathogenesis of major non-communicable diseases. The PGC-1α axis, the IL-6 exercise paradox, the irisin–adipose–bone–brain circuit, the myostatin–ActRIIB–SMAD atrophy program, and the emerging metabolokine biology of lactate, BAIBA, and kynurenic acid collectively constitute a biochemically coherent endocrine language through which physical activity communicates systemic health.

This paradigm carries immediate translational implications. First, exercise prescription must be conceptualized in endocrine pharmacological terms, with modality, intensity, volume, and timing selected to optimize specific myokine outputs for specific clinical objectives. Second, myokine mimetics—irisin analogs, anti-ActRIIB biologics, FGF21 analogs—represent a pharmacological strategy for patients unable to exercise adequately, with the important caveat that pharmacological myokine replacement is unlikely to recapitulate the full complexity of the exercising muscle secretome. Third, the emerging synergy between exercise-derived myokines and GLP-1 receptor agonist pharmacotherapy suggests that combinatorial regimens may achieve metabolic efficacy superior to either intervention alone. Ultimately, the muscle endocrine organ represents the evolutionary substrate for the health benefits of physical activity—a system shaped by millions of years of obligate locomotion that, in the sedentary modern environment, is chronically under functioned. Restoring its endocrine output, whether through behavioral or pharmacological means, is a rational and evidence-based strategy for addressing the global burden of cardiometabolic, neurodegenerative, and oncological disease.

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LIST OF ABBREVIATIONS

AMPK, AMP-activated protein kinase; ActRIIB, activin receptor type IIB; BAIBA, β-aminoisobutyric acid; BDNF, brain-derived neurotrophic factor; CaMKII, Ca^{2+}/calmodulin-dependent protein kinase II; EV, extracellular vesicle; FGF21, fibroblast growth factor 21; FNDC5, fibronectin type III domain-containing protein 5; GDF-8, growth differentiation factor 8 (myostatin); GLP-1, glucagon-like peptide-1; HDAC, histone deacetylase; IGF-1, insulin-like growth factor 1; IL, interleukin; JAK, Janus kinase; KAT, kynurenine aminotransferase; LIF, leukemia inhibitory factor; MASLD, metabolic dysfunction-associated steatotic liver disease; MEF2, myocyte enhancer factor 2; miRNA, microRNA; mTORC1, mammalian target of rapamycin complex 1; NAFLD, non-alcoholic fatty liver disease; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT, nuclear factor of activated T-cells; NK, natural killer; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; SMAD, small mothers against decapentaplegic; SPARC, secreted protein acidic and rich in cysteine; STAT3, signal transducer and activator of transcription 3; T2DM, type 2 diabetes mellitus; TGF-β, transforming growth factor beta; UCP-1, uncoupling protein 1; WAT, white adipose tissue; WAT browning, conversion of white to beige adipocytes.

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