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Review

The local–systemic axis of the skeletal muscle secretome

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Exercise stimulates the release of bioactive factors, termed exerkines, that contribute to local and systemic adaptation. Circulating exerkines are often interpreted as direct readouts of muscle secretion, overlooking regulatory processes within tissues that shape their production, transformation, and release. Using skeletal muscle and endurance exercise as a model system, we define a local–systemic secretome axis shaped by spatial organization, stimulus-specific programs, temporal dynamics, extracellular processing, and paracrine circuitry. By integrating evidence from recent transcriptomics, proteomics, interstitial fluid, and extracellular vesicle studies, we outline how these processes govern signal propagation from muscle to circulation and inform the interpretation of circulating exerkines as biomarkers and therapeutic targets.

Highlights

Circulating exerkines reflect selective export rather than total tissue secretion.

Local signaling networks shape the composition and fate of secreted factors.

Spatial, temporal, and extracellular constraints govern signal dissemination.

Interstitial compartments reveal a broader and more dynamic secretome.

Integrating local and systemic data is key to resolving exercise signaling.

From exerkines to intramuscular control

Exercise induces coordinated adaptations across multiple organ systems that extend beyond the immediate demands of energy expenditure, including metabolic remodeling, improved vascular function, immune modulation, and enhanced tissue resilience [1–3]. A central mechanism underlying these systemic adaptations is interorgan communication mediated by circulating signaling molecules released during and after exercise, collectively termed **exerkines** (see Glossary) (Box 1) [7,8]. Unlike **myokines**, which originate from skeletal muscle, exerkines encompass exercise-responsive signaling molecules released from multiple tissues. Prevailing models of exerkines often interpret plasma-detected factors as direct readouts of muscle **secretion**, overlooking a critical upstream layer of regulation within the tissue. Secretion occurs within a spatially organized, multicellular tissue environment in which parenchymal cells, endothelial cells, stromal populations, immune and other types of cells engage in dynamic paracrine interactions [1,13,14]. This complexity has become increasingly evident with advances in **single-cell/single-nucleus RNA sequencing**, which have revealed extensive cell-type-specific communication networks, highlighting the coordinated nature of exercise-induced signaling across distinct cellular compartments [9,10,15]. Further evidence demonstrates that **interstitial fluid (IF)** measurements in exercised rodent and human skeletal muscle reveal proteomic profiles that diverge from plasma, indicating that many secreted factors are locally retained or rapidly consumed within tissue [11,16]. Additionally, temporal exercise studies show that exercise-induced signals are released in distinct waves, with early, transient responses often failing to accumulate to detectable levels in systemic circulation, whereas other factors emerge over longer time scales associated with tissue remodeling [17,18]. These collective observations suggest that circulating exerkines represent a biased and transformed subset of locally produced molecules rather than a comprehensive reflection of tissue-level secretion.

As the complexity and diversity of the exerkine family continue to expand, a conceptual framework is needed to explain how local secretory processes give rise to organism-wide signals. Drawing primarily on evidence from skeletal muscle and endurance exercise studies, we define

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Box 1. From exercise factors to exerkines

The concept of exerkines can be traced to investigations from the mid-20th century that sought to identify putative 'exercise factors' responsible for the systemic effects of physical activity [2,4]. This idea evolved with the recognition of skeletal muscle as an endocrine organ and the subsequent emergence of the myokine paradigm, exemplified by the identification of IL-6 as an exercise-responsive cytokine capable of mediating communication beyond muscle [5,6]. As evidence accumulated, however, it became clear that exercise-induced communication extends beyond skeletal muscle. Signaling molecules responsive to physical activity are now recognized to originate from multiple tissues, including adipose tissue, liver, bone, heart, immune cells, and the vasculature [7,8]. As a result, a broader framework became necessary to capture the distributed nature of exercise-induced communication, leading to the adoption of the term *exerkine* to encompass exercise-responsive mediators irrespective of tissue origin. Exerkines can be defined as signaling molecules released in response to acute and/or chronic exercise that mediate communication through autocrine, paracrine, and endocrine pathways [7]. Although initially studied primarily in the context of endurance exercise, exerkine responses have now been documented across diverse exercise modalities, including resistance training [8]. As such, exerkines are not restricted to a single tissue, signaling range, or physiological function.

These advances reflect a fundamental shift in exercise biology. Rather than viewing adaptation as a consequence of a small number of circulating factors, contemporary models increasingly recognize exercise-induced communication as a distributed and highly integrated network operating across multiple tissues, cell types, and biological compartments [9–12]. Accordingly, exerkines are best viewed not simply as individual molecules but as a conceptual framework for understanding how exercise coordinates local and systemic adaptation through intercellular and interorgan communication.

a local–systemic secretome axis shaped by spatial organization, **extracellular filtering**, stimulus-specific programs, temporal stratification, and paracrine circuit dynamics. Within this framework, tissue-level signaling networks act as biological filters that determine which molecules remain within local microenvironments and which ultimately become detectable in the circulation. Circulating exerkines should, therefore, be interpreted as downstream outputs of tissue-level signal processing, underscoring the importance of incorporating local tissue context when evaluating a complete exercise response. This perspective is particularly timely given recent advances in single-cell and spatial omics, extracellular fluid proteomics, and systems-level approaches that now enable interrogation of local secretory networks with unprecedented resolution. Together, these advances provide an opportunity to connect tissue-resident signaling processes with systemic exercise adaptations across biological scales. Ultimately, understanding exercise adaptation requires studying not only the signals that enter the circulation but also the local networks from which they emerge.

Principles governing the secretome

Spatial organization of secretion

Spatial organization imposes a primary constraint on signal propagation within tissues by determining where signals originate and their proximity to the site of action. Skeletal muscle is organized into hierarchical anatomical compartments, including the endomysium and perimysium, as well as specialized interfaces linking muscle to neural and tendinous regions [1]. Within these compartments, anatomically defined regions, including perivascular spaces, interstitial stromal domains, neuromuscular junctions, myotendinous junctions, and intramuscular adipose depots, serve as spatially localized platforms for distinct **microenvironments**. These microenvironments are characterized by distinct cellular compositions, activation states, and extracellular matrix contexts, which give rise to region-specific transcriptional and signaling programs that vary in response to acute stimuli or chronic physiological conditions [19–21].

Within the muscle microenvironments, resident cell populations, including stromal, vascular, immune, and myogenic cells, function as spatially restricted secretory units that contribute distinct components to the local signaling milieu (Figure 1A). Stromal populations, particularly fibro–adipogenic progenitors (FAPs), exhibit substantial heterogeneity across anatomical sites and form functionally specialized subpopulations involved in regeneration, vascular remodeling, and extracellular matrix regulation [22–24]. These cells engage in reciprocal interactions with

Glossary

Exerkines: a heterogeneous class of bioactive molecules released from various tissues and organs in response to acute or chronic exercise, mediating signaling through endocrine, paracrine, and autocrine mechanisms.
Extracellular filtering: a set of extracellular processes, including matrix binding, proteolytic processing, and association with carrier proteins, that regulate signal retention, activation, and transport.
Extracellular vesicles (EVs): lipid bilayer–enclosed particles released by cells that transport proteins, lipids, and nucleic acids, contributing to intercellular communication and molecular exchange.
Interstitial fluid (IF): the extracellular fluid within tissues that serves as an intermediate compartment for locally secreted molecules prior to their potential entry into the circulation.
Local retention: the confinement of secreted molecules within tissue due to matrix binding, restricted diffusion, or cellular uptake, which limits their access to the circulation.
Microenvironments: spatially defined regions within a tissue, characterized by specific cellular composition, extracellular matrix context, and signaling activity.
Myokines: a subset of secreted proteins produced by skeletal muscle, acting locally and systemically to regulate physiological processes.
Paracrine circuits: multicellular signaling networks within tissues in which secreted factors are propagated, amplified, or transformed through interactions among neighboring cell populations.
Proteomics: the large-scale analysis of proteins, including their abundance, structure, post-translational modifications, and interactions, to define functional proteomes.
Secretion: the release of a molecule from a cell into the extracellular environment, regardless of whether it remains within the local tissue or enters the circulation.
Secretion kinetics: the rate and temporal dynamics of the release of signaling molecules, which influence their availability and detectability across local and systemic compartments.
Secretome: the complete set of molecules actively secreted by a cell, tissue, or organism, including proteins,

endothelial cells, immune populations, and myofibers, forming localized signaling networks that shape the composition of secreted factors within these microenvironments [13,14]. Emerging analyses further suggest that stromal and niche-resident populations represent major contributors to the exercise-responsive **secretome** [9,10]. Critically, the spatial positioning of these cells influences whether released factors are retained within local signaling networks or positioned for vascular access and systemic export.

Spatial organization, therefore, constitutes an initial constraint layer within the intramuscular secretory system. Signals produced in perivascular regions or by vascular-associated cells are inherently positioned for efficient entry into the circulation, whereas signals generated in deeper interstitial compartments are more likely to undergo **local retention**, consumption, or transformation prior to reaching the vasculature. Consequently, molecules with similar production rates may differ substantially in their endocrine visibility based solely on their site of origin. Spatial organization thus biases which signals are retained within local paracrine networks and which are permitted to progress toward **systemic dissemination**.

Extracellular processing and release constraints

Following secretion, signaling molecules encounter multiple layers of regulation within the extracellular space that govern their availability, processing, and transport (Figure 1B). Rather than diffusing freely, many factors interact with extracellular matrix components, including proteoglycans, which can sequester ligands, restrict their mobility, and establish localized concentration gradients [25,26]. These interactions create spatially confined reservoirs of growth factors and cytokines, limiting immediate access to the vasculature and imposing a constraint on endocrine dissemination. For example, vascular endothelial growth factor (VEGF) binds heparan sulfate proteoglycans within the matrix, generating spatial gradients that guide angiogenic signaling and limit diffusion toward the vasculature [27,28]. Additional matricellular proteins, such as osteonectin and decorin, can interact with extracellular matrix components to regulate matrix organization and growth factor availability, contributing to local retention and modulation of signaling within the tissue [28].

Proteolytic remodeling of the extracellular matrix can liberate or activate matrix-bound and latent factors, thereby linking ligand availability to dynamic tissue states such as mechanical loading, inflammation, and repair [25]. This process is mediated in part by matrix metalloproteinases (MMPs), whose activity is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs). Contractile activity, mechanical loading, tissue injury, and inflammatory signaling can alter the balance between MMPs and TIMPs, resulting in context-dependent extracellular matrix remodeling and the mobilization of matrix-sequestered signaling molecules [5,29]. For example, transforming growth factor-beta (TGF-β) is sequestered in a latent complex within the matrix and requires context-dependent activation for release, enabling tight spatial and temporal control of its signaling activity [26]. Extracellular matrices can also function as reservoirs for numerous bioactive signaling molecules, including bone morphogenetic proteins (BMPs), insulin-like growth factors (IGFs), and fibroblast growth factors (FGFs). These secretory factors are stored within the extracellular matrix and can be liberated during remodeling and mechanical loading [25,28]. Through these mechanisms, extracellular environments dynamically control both the timing and extent of signal release. In parallel, signals are partitioned into distinct extracellular routes that influence their capacity to exit the tissue. In addition to matrix interactions, ligands within the extracellular space can associate with soluble receptors and binding proteins [e.g., interleukin-6 (IL-6) with soluble IL-6 R/gp130; myostatin with follistatin], thereby modulating their diffusion, stability, and signaling activity [30,31]. While such interactions are well established in circulation, several of these binding factors have also been detected in the IF of muscle, suggesting that a similar regulatory layer may operate within the extracellular domain [11,18]. While some factors are released

peptides, lipids, metabolites, and vesicle-associated factors involved in intercellular communication.
Single-cell/single-nucleus RNA sequencing: techniques that profile gene expression at cellular resolution, enabling the identification of cell-type-specific signaling programs.
Systemic dissemination: the process by which locally produced signaling molecules are exported beyond the tissue microenvironment and enter the circulation, enabling potential communication with distant tissues.
Systemic detection: measurement of a signaling molecule in blood or other biofluids, representing the subset of secreted factors that persist through local retention, transport, and clearance processes.
TurboID: an engineered biotin ligase-based proximity labeling system that catalyzes rapid biotinylation of nearby proteins, enabling spatially resolved protein identification and enrichment.

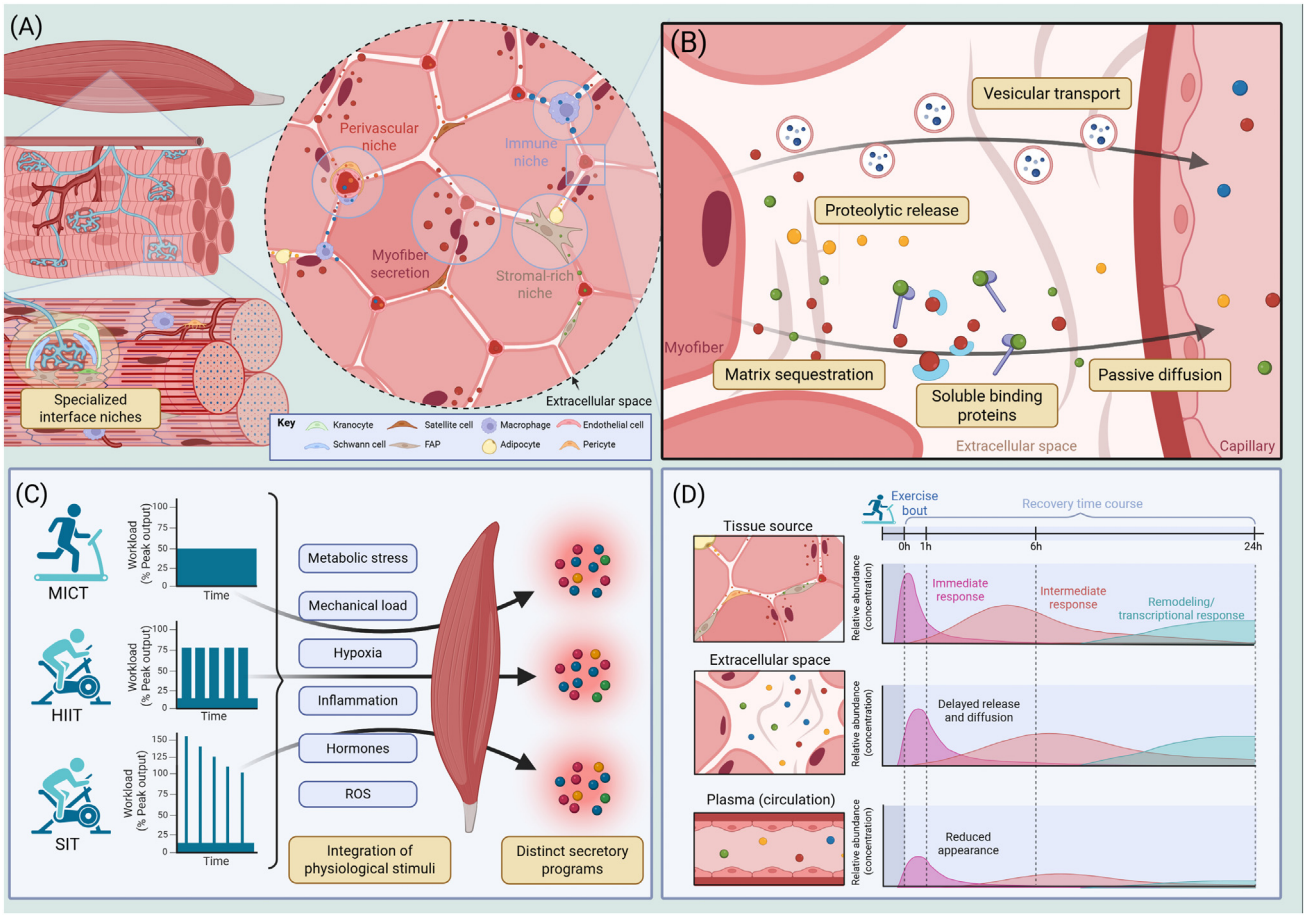

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Figure 1. Principles governing production, processing, and selective export of the exercise secretome. The composition of the intramuscular secretome is determined by a series of layered constraints that act on locally produced factors prior to their appearance in circulation. (A) Spatial organization constrains signal propagation by determining the site of origin within anatomically distinct microenvironments. Signals generated in perivascular regions are positioned for efficient vascular access, whereas those produced in deeper interstitial compartments are more likely to be retained, consumed, or transformed locally. (B) Extracellular processing further regulates signal availability through matrix sequestration, proteolytic activation, association with soluble binding partners, and partitioning into distinct transport routes, including extracellular vesicles. For example, matrix-associated factors (e.g., periostin, musculoskeletal embryonic nuclear protein 1, and osteonectin) may be retained within extracellular microenvironments, whereas soluble cytokines such as IL-6 are rapidly released and cleared. Extracellular vesicles can additionally transport proteins, lipids, and microRNAs while protecting cargo from degradation, whereas endocrine exerkines capable of efficient vascular access and systemic stability are more readily detected in plasma. (C) Stimulus specificity defines the input layer, where distinct physiological cues, including metabolic stress, mechanical load, hypoxia, inflammation, hormonal signals, and reactive oxygen species (ROS), induce stimulus-specific secretory programs. (D) Temporal stratification imposes kinetic constraints on signal detectability, as sequential waves of secretion are differentially captured depending on their timing relative to local utilization and systemic clearance. Together, these layers progressively filter the pool of secreted factors, such that circulating exerkines represent a selective subset of locally produced signals rather than a direct reflection of total secretion. Colored particles represent secreted factors, and arrows denote directional propagation and potential routes of signal dissemination. Illustrated in skeletal muscle but conceptually applicable to other tissue secretomes. Figure created with BioRender. FAP, fibro–adipogenic progenitor; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; SIT, sprint interval training.

in soluble form and diffuse within the interstitial space, others are retained locally or packaged into **extracellular vesicles (EVs)**, which can delay, protect, or spatially direct their propagation (Box 2) [7]. These parallel routes and diverse molecular classes of the secretome introduce heterogeneity in signal transport, such that molecules with similar production rates may differ substantially in their likelihood of reaching the circulation. Together, these extracellular processes define a final regulatory layer that determines whether locally produced signals are retained, activated, or exported.

Box 2. Molecular classes and transport logic of exercise-induced signals

Exerkines comprise diverse molecular classes, including proteins, peptides, metabolites, lipids, and EVs [7,32]. These distinct molecular identities confer specific physicochemical properties that constitute a primary regulatory layer governing how exercise-induced signals are stabilized, distributed, and ultimately detected. Proteins and peptides, including many cytokines, are typically released in soluble form and can readily access the vasculature; however, their systemic profiles are constrained by rapid turnover, receptor-mediated uptake, and proteolytic degradation [33], such that circulating concentrations often reflect dynamic secretion–clearance equilibria rather than steady-state production [34,35]. Metabolites often follow a different transport logic from classically secreted factors: their circulating levels reflect integrated interorgan metabolic flux [12,16,36], although some metabolites, for example, 3-Aminoisobutyric acid (BAIBA), are directly regulated by exercise [37]. In contrast, lipids exhibit intermediate transport behavior, often circulating bound to carrier proteins or within lipoprotein particles, which influences their stability, distribution, and signaling range [38,39]. EVs represent a specialized transport modality in which bioactive cargo is encapsulated within membrane-bound vesicles, enabling protection from degradation, prolonged persistence, and, in some contexts, targeted delivery to recipient cells; notably, exercise modulates both the abundance and molecular composition of circulating EVs, supporting their role as regulated vectors of interorgan communication [40,41]. Compared with freely soluble factors, EV packaging can alter temporal signaling kinetics by extending cargo stability and reducing clearance, while vesicle surface composition may influence biodistribution, cellular uptake, and the persistence of signals within the circulation. Collectively, these transport regimes impose a functional hierarchy on the secretome, wherein signals that are stable, protected, or efficiently transported are more likely to enter and persist in the circulation, whereas those that are rapidly degraded, sequestered, or locally consumed remain confined to tissue-level signaling networks. Circulating exerkine profiles are therefore intrinsically biased toward molecules with favorable transport characteristics, reinforcing that plasma measurements represent selectively exported outputs rather than comprehensive readouts of intramuscular signaling activity.

Stimulus specificity of secretory programs

The composition of the intramuscular secretome is specified by the initiating physiological stimulus, which defines the input layer of the system. Skeletal muscle integrates diverse cues, including contractile activity, mechanical load, metabolic stress, hypoxia, inflammatory signals, and systemic hormonal inputs, each of which activates distinct intracellular signaling pathways and transcriptional programs (Box 3) [1,3]. Rather than uniformly increasing secretion, these inputs generate stimulus-specific secretory programs that determine the composition and functional roles of released factors (Figure 1C).

Contractile and metabolic stress promote the release of factors involved in substrate utilization, mitochondrial adaptation, and vascular regulation, whereas inflammatory or damage-

Box 3. Regulatory control of secretome release during exercise

The exercise-induced secretome is governed by a multilayered regulatory architecture that controls signal initiation, processing, and export. As these layers specify how exerkines are synthesized and trafficked for secretion, they shape the likelihood of entering local versus systemic signaling circuits [7]. During stimulus-dependent activation, muscle contraction triggers rapid intracellular signaling cascades that initiate secretory programs [1,3]. Transient increases in intracellular Ca^{2+}, shifts in cellular energy state reflected by AMP/ATP ratios, the accumulation of ROS, and mechanical loading stimuli collectively converge on key signaling nodes, including calcium/calmodulin-dependent protein kinase (CaMK), calcineurin, AMP-activated protein kinase (AMPK), mechanistic target of rapamycin complex 1 (mTORC1), and mitogen-activated protein kinase (MAPK) pathways. These pathways intergrate metabolic and mechanotransductive cues to engage overlapping yet distinct transcriptional networks that ultimately contribute to secretory regulation across exercise modalities. Among the best-characterized regulators is peroxisome proliferator-activated receptor gamma coactivator 1-α (PGC-1α), which links metabolic stress to coordinated transcriptional remodeling and secretory output [42,43]. PGC-1α and related coactivators establish context-dependent transcriptional programs that influence secretome-related genes, with the relative contribution of these pathways shaped by exercise modality, intensity, duration, and cell type [42,44]. Importantly, transcription is not equivalent to secretion: mRNA abundance must be coupled to translational efficiency, ribosomal loading, and protein turnover, introducing a critical regulatory filter between gene expression and secreted output [45,46]. Secreted factors are further refined through post-translational processing, which governs their bioactivity, stability, and interaction potential. For example, proteolytic cleavage can activate latent precursors or liberate matrix-bound factors [26,28,47,48], while glycosylation and other modifications influence protein folding, receptor binding, and resistance to degradation [49]. Finally, trafficking and export routing determine whether and how signals exit the cell. Proteins may be directed through the conventional endoplasmic reticulum (ER)–Golgi pathway or diverted into nonclassical routes, including EVs and autophagy-associated secretion [50,51]. Exercise-induced perturbations, such as ER stress and remodeling of vesicular trafficking networks, can reprogram these pathways, altering both the mode and efficiency of export of secreted factors [7,34,41,52]. Consequently, molecules with comparable intracellular abundance can differ substantially in their probability of release and their eventual distribution between local tissue microenvironments and the circulation [11,53].

associated signals induce cytokines and mediators of tissue repair and immune recruitment [1]. A well-characterized example is IL-6, whose release is modulated by metabolic state and exercise intensity, with greater secretion observed under conditions of glycogen depletion [5]. Signal composition is further shaped by the intensity and duration of the stimulus, such that exercise modalities, including moderate-intensity continuous training (MICT), sprint interval training (SIT), high-intensity interval training (HIIT), or resistance training, produce partially overlapping yet also clearly distinct secretory responses. Recent large-scale human multiomic studies of circulating plasma support this framework, demonstrating that different exercise regimens generate both shared and modality-specific systemic signatures [17,29,54–56].

Within the local–systemic secretome axis, stimulus specificity defines the input layer by determining which signals are initiated and subsequently subjected to downstream spatial, temporal, and extracellular constraints. Circulating exerkines, therefore, reflect not only the presence of muscle activity but also the nature of the underlying physiological stimulus that shapes the pool of signals available for systemic dissemination.

Temporal stratification of secretory responses

Secretion is further modulated by temporal stratification. As exercise-induced signaling unfolds across multiple time scales, sequential waves of secreted molecules are produced during and after muscle activity [18,55,56]. This temporal structure imposes a constraint on signal detectability, as circulating abundance depends on **secretion kinetics** relative to local utilization and systemic clearance (Figure 1D). Early-phase signals emerge during or immediately following contraction and contribute to the acute physiological response of metabolic coordination, vascular regulation, and immune cell recruitment. These signals encompass multiple molecular classes, including cytokines and growth factors [e.g., IL-6, CXCL1, and leukemia inhibitory factor (LIF)], metabolites (e.g., lactate), and EVs, which are rapidly released during or shortly after exercise and influence local and systemic signaling networks [5,12,56,57]. In contrast, delayed secretory responses arise hours to days later through transcriptionally driven programs that support structural and metabolic remodeling, including angiogenesis, extracellular matrix reorganization, mitochondrial biogenesis, and immune resolution [56,58]. Time-resolved proteomic studies demonstrate exercise-induced biphasic patterns of factor release into both the interstitial space and circulation, indicating that distinct temporal waves are differentially captured across various biofluid compartments [17,18,29,56,59]. Consistent with this, transcriptomic analyses reveal temporally stratified induction of predicted secreted factors across various cell types in exercised muscle [9].

Circulating abundance, therefore, reflects the balance between secretion and systemic clearance, as well as the temporal alignment between these two processes. Plasma measurements capture time-dependent snapshots of an evolving signaling process rather than cumulative secretion, such that transient or rapidly consumed signals may fail to accumulate to detectable levels despite substantial local activity. Temporal stratification thus imposes kinetic constraints on endocrine visibility, biasing **systemic detection** toward signals with sustained release or slower clearance kinetics.

Paracrine circuitry and selective export shape the systemic secretome

While these principles define the constraints governing the production, timing, and dissemination of secreted factors, they do not fully capture how these signals function within tissue. In the context of skeletal muscle, the functional effects of the intramuscular secretome are executed through multicellular **paracrine circuits**, which govern how signals are propagated, integrated, and transformed prior to systemic dissemination (Figure 2) [13,14]. Primary cellular signals are

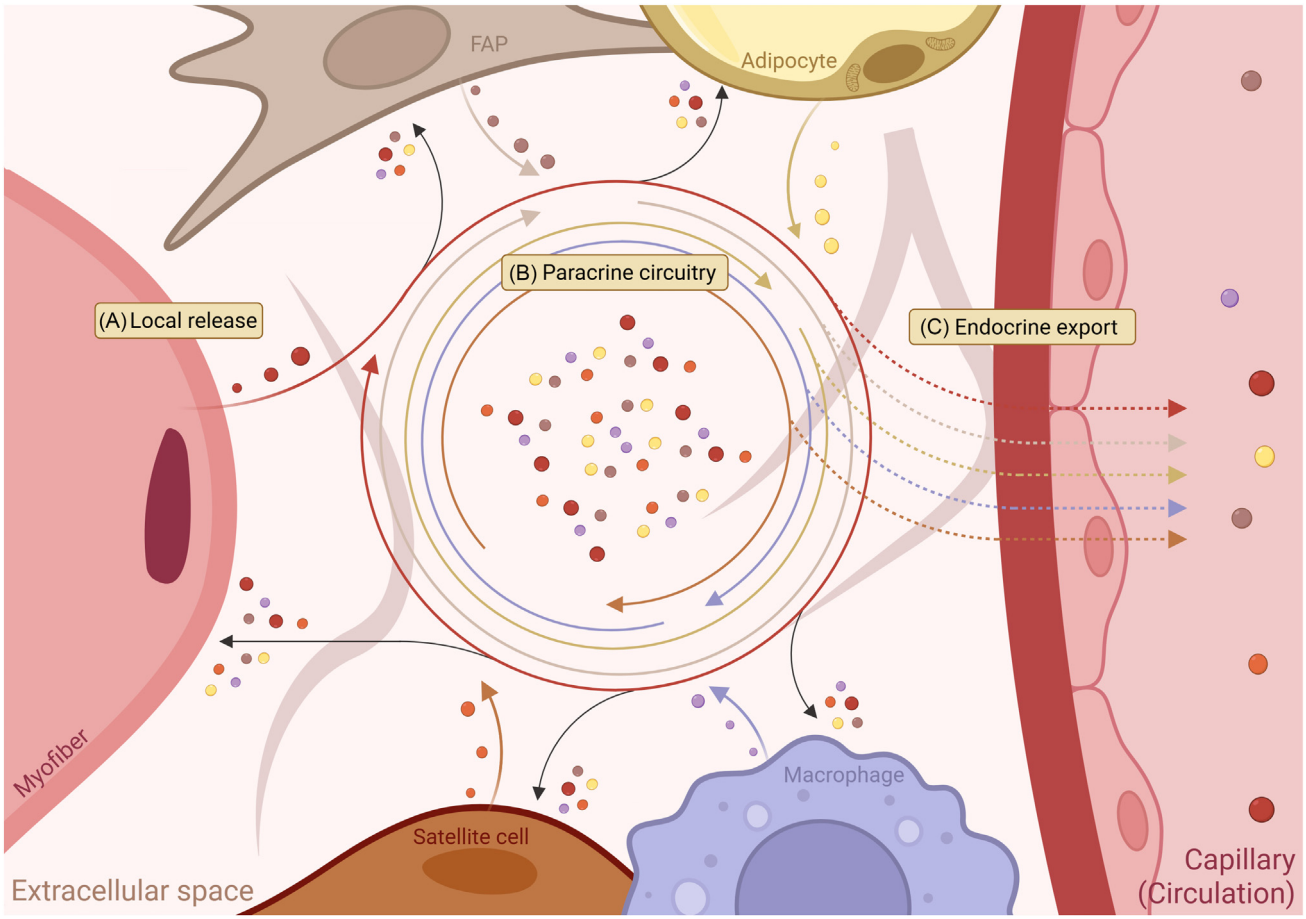

Figure 2. Multicellular processing and selective export of the intramuscular secretome. The intramuscular secretome is organized as a multicellular signaling network that integrates, transforms, and selectively exports locally produced factors to the circulation. (A) Contracting myofibers release myokines into the extracellular space, where signals act locally within the tissue microenvironment. These factors engage neighboring cell types through paracrine signaling and can also act on the myofiber via autocrine feedback. (B) Nonmyofiber cell populations, including fibro–adipogenic progenitors (FAPs), adipocytes, macrophages, and satellite cells, represent additional sources of secreted factors within muscle tissue. Their secretory activity may be directly induced by contractile stimuli or secondarily activated through paracrine cues, generating sequential waves of signaling that amplify and reshape the initial response, as illustrated by the concentric rings. (C) A selective subset of factors is transferred across the endothelial barrier into the circulation, where they contribute to systemic endocrine signaling targeting distant tissues. This export reflects the balance between local retention, interstitial processing, and vascular accessibility rather than total production. Colored molecules represent secreted factors, with color indicating the cell type of origin. Arrows denote directional signal propagation, with solid arrows indicating local interstitial signaling and dashed lines representing transfer toward and across the vasculature. Figure created with BioRender.

frequently amplified through the recruitment and activation of secondary cell populations, generating cascades of secondary secretion that reinforce and expand the initial response. Additionally, signals can be further reshaped through receptor-mediated uptake and feedback interactions, which modulate signal intensity, duration, and downstream effects.

These dynamics are evident across multiple physiological circumstances. In angiogenic remodeling, signaling between muscle and vascular compartments drives coordinated adaptation through reciprocal activation and reinforcement, as observed in VEGF-, NOTCH-, or angiopoietin (ANGPT)-mediated myofiber–endothelial signaling [60,61]. During tissue repair, early inflammatory signals are amplified and subsequently transformed into regenerative programs through sequential interactions among immune and progenitor populations, including macrophage–

satellite cell–FAP signaling cascades involving chemokine-driven immune recruitment, cytokine-mediated myogenic activation, and growth factor-dependent stromal remodeling [14,62]. At the neuromuscular junction, highly coordinated signaling interactions maintain synaptic stability through tightly regulated local communication, exemplified by neural growth factors, IL-6, FGFs, brain-derived neurotrophic factor, or neurturin signaling pathways [63–65]. Other intramuscular niches, including the myotendinous junction [66], intramuscular adipose tissue [67], and additional specialized microenvironments, were recently resolved through spatial and single-cell approaches. Across these dedicated contexts, circuit behavior enables both signal propagation and functional specialization within tissue.

Critically, these specialized paracrine circuits function as integrative filtering systems that determine the fate of secreted molecules within tissue. Through local consumption, feedback regulation, and signal transformation, these circuits regulate whether signals are amplified within local networks or permitted to progress toward systemic dissemination. As a result, a substantial fraction of muscle-derived signaling remains confined within intramuscular circuits rather than contributing to circulating pools. Interstitial sampling demonstrates that secreted factors accumulate within the muscle microenvironment at concentrations exceeding those observed in plasma; for example, interstitial IL-6 increases markedly during exercise without proportional changes in circulation [68,69]. Consistent with this, interstitial and extracellular fluid analyses demonstrate that a large proportion of biologically active signals are enriched locally compared to circulation, indicating that the functional secretome is broader and more compartmentalized than inferred from plasma measurements alone [11,16]. More recent proteomic analyses reveal a distinct repertoire of extracellular proteins and metabolites enriched within IF following exercise [16,18]. In this context, circulating exerkines are best understood not as direct proxies of muscle-derived secretion but as selective outputs of intramuscular signaling systems. Only a subset of locally produced molecules traverse tissue-level constraints to reach the circulation, such that circulating abundance reflects not only production but the combined effects of local retention, consumption, biochemical transformation, transport, and systemic clearance. Consequently, plasma profiles are inherently biased toward molecules with favorable export and persistence characteristics, while underrepresenting signals that act predominantly within tissue. Distinct transport modalities, including freely diffusible factors and EV-associated cargo, further shape which signals can access systemic compartments (Box 2). These findings support a model in which interstitial signaling represents a primary phase of muscle-derived communication, with systemic appearance reflecting a selective downstream process. A comprehensive understanding of the muscle secretome will therefore require interrogation of local biofluid compartments in addition to circulation to capture the full breadth of muscle-derived signaling.

Beyond the level of the tissue, circulating profiles are further shaped by temporal and molecular filtering. Exercise induces phase-specific waves of secretion that are unevenly captured depending on sampling time (e.g., during exercise, immediately after, or during recovery phases) [17,18,55,56]. Circulating profiles provide only partial coverage of the secretory response when sampling does not span the full time course. These dynamics have been recently documented through large-scale human metabolomics and proteomic studies, including datasets from the Molecular Transducers of Physical Activity Consortium (MoTrPAC) and HEalth, RIsk factors, exercise Training And GEnetics (HERITAGE) trials, which delineate acute and time-resolved responses to exercise stimuli [17,55,59].

Advances in plasma **proteomics** have substantially increased detection depth but do not overcome intrinsic biological filtering [70]. High-depth plasma proteomic platforms (e.g., PreOmics, Olink, SomaScan, and Seer) enable sensitive measurement of targeted protein panels from minimal biofluid input; however, detectable signals remain shaped by both biological constraints

and panel-specific biases. Emerging proteomic strategies now enable cellular resolution, including cell-type-specific labeling approaches based on proximity-dependent biotin ligases and related systems (e.g., **TurboID** and MetRS*-based methods) [34,71–73]. These approaches have demonstrated the capacity to trace muscle-derived proteins, as well as other tissue-specific origins, from defined cellular sources into circulation, providing direct evidence that circulating profiles represent selective outputs of underlying tissue processes [34,73].

A contemporary view of circulating exerkines considers these factors not as direct readouts of muscle secretion but as emergent outputs of a constrained and compartmentalized signaling system shaped by spatial, temporal, and molecular filtering within tissue. Accordingly, plasma measurements capture a biased and time-dependent snapshot of an evolving secretory landscape rather than a comprehensive readout of muscle-derived secretion. This framework has important implications for biomarker discovery and interpretation, as circulating profiles may systematically underrepresent biologically important signals that remain locally confined, matrix-bound, or rapidly consumed within tissue microenvironments. Interpreting circulating profiles within this framework clarifies the relationship between local signaling dynamics and systemic measurements and highlights the limitations inherent to plasma-centric analyses.

Resolving the local–systemic secretome axis through experimental and computational integration

Determining how exercise-induced signals are retained, processed, and secreted across biological compartments requires the integration of complementary experimental and computational approaches. A fundamental challenge is that transcriptional activation does not necessarily predict secretion, as induced transcripts may not undergo efficient translation, processing, extracellular release, vascular transport, or systemic accumulation. Consequently, no single experimental modality provides a complete view of exercise-induced signaling. Single-cell and spatial transcriptomic approaches identify candidate cellular and anatomical sources of secreted factors, whereas tissue, IF, and circulating proteomic measurements capture distinct stages of the secretory process. Confidence in candidate exerkines is therefore strengthened when evidence converges across multiple molecular layers and biological compartments [16,55,74].

Integrating these datasets presents important computational challenges. Spatial transcriptomics can localize sites of signal production, but transcript localization does not necessarily correspond to the distribution of secreted proteins. Likewise, ligand–receptor inference frameworks such as CellChat, CellPhoneDB, LIANA, and NicheNet can identify potential signaling interactions but cannot independently determine whether a ligand remains locally restricted or achieves endocrine dissemination. For example, factors detected within tissue and IF but absent from circulation may be locally retained or rapidly consumed, whereas concordant detection across tissue, extracellular fluid, and plasma compartments would provide stronger evidence for systemic export. Integration of spatial, proteomic, and cell–cell communication datasets will therefore be critical for distinguishing local retention from systemic dissemination.

Temporal resolution represents an equally important consideration. Transcriptomic, proteomic, and circulating responses often occur on different timescales, such that molecular changes may not align temporally across datasets. Moreover, exercise induces distinct transcriptional responses across early-, intermediate-, and late-recovery phases, which may contribute to delayed or asynchronous protein secretion and systemic appearance [58,75]. Reliance on a single post-exercise sampling time point is, therefore, unlikely to capture the complexity of secretome dynamics. Although optimal sampling schedules will depend on the biological question and molecule under investigation, studies may benefit from sampling before exercise, during

exercise where feasible, immediately after exercise, and at delayed recovery time points (e.g., 1 h, 6 h, and 24 h). Where feasible, parallel sampling of tissue, IF, and circulation may further facilitate discrimination between local signaling events and factors that achieve meaningful systemic dissemination. Such integrated approaches will improve the interpretation of circulating biomarkers and the prioritization of therapeutic exerkine candidates.

Concluding remarks and future perspectives

Exercise-induced interorgan communication is governed not simply by the identity or abundance of secreted factors, but by layered constraints that regulate their production, transformation, and export within tissue. Spatial organization, stimulus-specific programs, temporal dynamics, extracellular processing, and paracrine circuitry together define an integrated architecture that determines which locally produced signals are retained, reshaped, or released into the circulation. Within this local–systemic secretome axis, circulating exerkines represent selective, time-dependent outputs of intramuscular signaling networks rather than direct readouts of myofiber secretion. Plasma-based measurements, therefore, provide an inherently incomplete view of the secretory response and must be interpreted in the context of tissue-level dynamics, requiring approaches that resolve spatial, cellular, and temporal dimensions of secretion across interstitial and systemic compartments.

A central priority for the field is to resolve the muscle secretome within its native spatial, cellular, and temporal context (see Outstanding questions). Although this review focuses on skeletal muscle, many of the principles underlying the local–systemic secretome axis may provide a useful framework for understanding communication across other exercise-responsive tissues and interorgan networks. For example, those networks are necessary for the coordination of load-bearing capacity (e.g., bone, tendons, and muscle), substrate availability and metabolism (e.g., liver, adipose tissue, and muscle), oxygen availability (e.g., heart, vasculature, and muscle), or regulation of performance and avoidance of overexertion (e.g., brain, afferent systems, and muscle). Determining the extent to which these regulatory principles are conserved across tissues and altered by aging, disuse, and musculoskeletal disease represents an important future direction.

Achieving this goal will require approaches capable of interrogating local secretory environments across diverse biological contexts. However, the feasibility of such measurements will differ between tissues. While IF sampling is becoming increasingly feasible in skeletal muscle, application to structurally complex tissues, such as bone, may require alternative experimental strategies. Emerging cell-type-specific labeling approaches and molecular imaging modalities may, therefore, prove particularly valuable for resolving local–systemic signaling relationships in less accessible tissues (at least in humans) and for visualizing tissue remodeling, inflammation, stromal activation, receptor dynamics, and extracellular matrix remodeling *in vivo*.

Interpreting circulating exerkines within the context of the local–systemic secretome axis may improve biomarker discovery by distinguishing signals that are efficiently exported and systemically detectable from those that remain locally confined despite important biological functions. A deeper understanding of tissue-level filtering may likewise improve the prioritization of therapeutic exerkine candidates by identifying molecules capable of achieving physiologically meaningful autocrine, juxtacrine, paracrine, or endocrine actions. Together, these advances shift the field from cataloging circulating factors toward resolving the organizational logic of tissue-level signaling systems. With the convergence of spatial, temporal, and cell-type-resolved technologies, exerkine biology is moving beyond plasma-centric models toward integrated frameworks of secretion. Ultimately, defining how signals are structured, regulated, and selectively propagated across the local–systemic secretome axis will be essential for understanding how exercise

Outstanding questions

How do distinct intramuscular cell types contribute to the secretome across physiological contexts?

What are the spatial and biochemical mechanisms that regulate extracellular processing, retention, and release of secreted factors *in vivo*?

How are temporally stratified waves of secretion coordinated across cell types, and how do these dynamics translate into circulating profiles?

What determines whether a secreted factor remains locally confined within paracrine circuits versus achieves endocrine dissemination?

Which secreted factors exert their primary function locally within muscle, and which achieve physiologically meaningful endocrine effects?

To what extent do circulating exerkines reflect primary secretion versus secondary or systemic responses?

How do aging, disease, disuse, and tissue remodeling reshape the balance between local signal retention, extracellular processing, and systemic export?

Are the organizational principles of the local–systemic secretome axis conserved across other exercise-responsive and mechanically adaptive tissues?

confers systemic benefits and for translating these insights into biomarkers and targeted interventions across health, aging, and disease.

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Declaration of interests

The authors declare no competing interests.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (OpenAI) in order to assist with language editing, readability, manuscript organization, and text revision. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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