

Review Article

Artificial intelligence in decoding muscle–organ crosstalk: Unveiling myokine networks and therapeutic frontiers

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Abstract

Skeletal muscle functions as an endocrine organ, secreting myokines that mediate crosstalk with organs like the brain, liver, adipose tissue, and vascular system, influencing metabolism, inflammation, and disease progression. Advances in artificial intelligence (AI) are revolutionizing our ability to decode these complex interactions by predicting novel myokines, modeling signaling networks, and identifying therapeutic targets. Exercise training plays a pivotal role in modulating myokine expression, with both aerobic and resistance exercise inducing small to large increases in circulating myokines immediately to 60 minutes post-exercise, though levels typically return to baseline within hours. Different exercise modalities (resistance, aerobic, concurrent, high intensity interval training) stimulate distinct myokine profiles. These exercise-induced myokines contribute to improved metabolic regulation, muscle regeneration, and systemic health benefits, underscoring the therapeutic potential of tailored exercise interventions mediated through myokine signaling networks. This review explores how machine learning and network analysis tools bridge gaps in understanding myokine dynamics, particularly in exercise-induced contexts and pathologies such as obesity, cancer, and neurodegeneration. By integrating multi-omics data, AI-driven approaches offer unprecedented insights into myokine-mediated organ communication and their potential as biomarkers or treatments.

Key Words: Myokine, Artificial intelligence, Muscle, Organ crosstalk

Introduction

Skeletal muscle, long recognized for its mechanical role in movement, has emerged as a dynamic endocrine organ capable of systemic regulation through myokines-muscle-derived signaling proteins released during contraction (Severinsen & Pedersen, 2020). These molecules mediate crosstalk with distant organs, including the brain, liver, adipose tissue, and vascular system, modulating processes such as glucose homeostasis, neuroprotection, and immune responses (Kostka et al., 2024). Exercise-induced myokines, such as irisin and interleukin-6 (IL-6), exemplify this interplay: irisin enhances adipose tissue browning and bone formation, while IL-6 exhibits context-dependent roles in tumor suppression and neuroinflammation (Shao et al., 2024). Despite progress, the sheer complexity of myokine networks-spanning over 3,000 potential mediators-poses challenges in mapping their spatiotemporal dynamics, predicting tissue-specific effects, and translating findings into therapies for conditions like obesity, cancer, and neurodegenerative diseases (Shao et al., 2024).

Traditional reductionist approaches struggle to disentangle these interactions due to the nonlinear relationships between myokine secretion, organ-specific receptor expression, and downstream metabolic or inflammatory cascades (Shao et al., 2024). For instance, myostatin inhibits muscle growth while simultaneously promoting bone resorption, and brain-derived neurotrophic factor (BDNF) enhances synaptic plasticity but requires precise regulation to avoid paradoxical effects in cancer progression. This complexity is compounded by the bidirectional nature of crosstalk, as seen in muscle-kidney interactions where irisin rescues metabolic reprogramming in damaged renal tubules, thereby attenuating fibrosis (Peng et al., 2017).

Artificial intelligence (AI) offers transformative solutions to these challenges. Machine learning algorithms excel at identifying patterns in multi-omics datasets, enabling the prediction of novel novel myokines like musclin and METRNL, which regulate muscle repair and bone metabolism (Severinsen & Pedersen, 2020). Network analysis tools, such as VOSviewer,

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map keyword co-occurrence across decades of research, revealing underexplored pathways like myokine-mediated vascular normalization in tumors or AMPK-dependent anti-inflammatory signaling in adipose tissue. Deep learning models further simulate myokine behavior across biological barriers, predicting how factors like cathepsin B (CTSB) and IGF-1 traverse the blood-brain barrier to influence neurogenesis (Kostka et al., 2024).

The therapeutic implications are profound. AI-driven models have identified exercise-responsive myokines that suppress tumor growth via immune cell recruitment (e.g., oncostatin M) or reverse neurodegeneration by enhancing mitochondrial biogenesis in neurons (Kostka et al., 2024). Federated learning frameworks now integrate heterogeneous datasets to optimize personalized exercise prescriptions, while generative AI designs synthetic myokine analogs with enhanced stability for targeted delivery. However, challenges persist in validating these predictions in human-specific contexts and addressing ethical considerations around data privacy and AI-biomarker commercialization (Kostka et al., 2024). This review synthesizes breakthroughs at the AI-muscle interface, highlighting how computational tools are rewriting our understanding of organ crosstalk and forging new frontiers in precision medicine (see Table 1).

AI-driven myokine discovery and characterization

These AI models prioritize candidate myokines based on features like structural motifs indicative of secretion potential, tissue-specific expression patterns, and predicted interaction networks. This computational prioritization accelerates experimental validation by focusing efforts on the most promising targets, thereby streamlining the discovery pipeline in preclinical models. Data science (DS) approaches integrate supervised and unsupervised learning methods alongside protein interaction and gene network analyses (e.g., using tools like STRING, GeneMANIA, HumanNet) to build comprehensive interaction maps of the muscle secretome. Such integrative analyses have identified both well-established and putative myokines, many of which are carried in extracellular vesicles, suggesting complex modes of inter-organ signaling (Gao et al., 2024).

Furthermore, AI-driven multi-omics integration enables the modeling of exercise-responsive myokine networks, revealing how different exercise modalities (e.g., resistance vs. cardiovascular training) modulate myokine secretion profiles that influence musculoskeletal aging, cognitive function, and systemic metabolism (Kostka et al., 2024; Li et al., 2024). For example, machine learning helps elucidate how key myokines like IL-6, BDNF, irisin, and IGF-1 are regulated and interact within these networks.

Overall, AI-powered discovery and characterization of myokines

provide unprecedented insights into their molecular signatures, secretion dynamics, and functional roles in muscle-organ crosstalk (Figure 1). This accelerates the identification of novel biomarkers and therapeutic targets for metabolic, neurodegenerative, and musculoskeletal diseases, enabling precision interventions informed by data-driven predictions (Kostka et al., 2024).

Modeling myokine-organ networks

Modeling the complex networks of myokine-mediated communication between skeletal muscle and other organs is a critical frontier in understanding systemic physiology and disease. Network analysis tools such as VOSviewer enable the mapping of keyword co-occurrence in scientific literature, revealing research trends and focal points, for example, in muscle-adipose tissue crosstalk, thermogenesis, and obesity (Letukienė et al., 2024). These bibliometric approaches highlight the evolving landscape of myokine research, showing how specific myokines are implicated in metabolic regulation and disease states.

AI further advances this field by integrating diverse multi-omics datasets-transcriptomics, proteomics, metabolomics-to simulate and predict myokine signaling pathways and their systemic effects. For instance, AI-driven network models can capture the dual role of interleukin-6 (IL-6), a well-studied myokine, which can promote tumor regression or progression depending on the biological context and interacting pathways. Such models use machine learning algorithms to analyze protein-protein interaction networks (e.g., STRING, GeneMANIA) and gene co-expression data to identify both established and putative myokines, expanding the known muscle secretome (Bondi et al., 2023).

These computational frameworks allow researchers to:

- Predict novel myokines and their target organs.
- Map signaling cascades and feedback loops that regulate metabolic, inflammatory, and regenerative processes.
- Identify potential biomarkers for diseases like obesity, cancer, and neurodegeneration.
- Suggest therapeutic targets by simulating interventions in myokine networks.

By combining supervised and unsupervised learning methods, AI tools provide a comprehensive, data-driven approach that complements expert knowledge, enabling the exploration of complex muscle-organ crosstalk at a systems biology level. This integrative modeling is especially powerful in contexts such as exercise physiology, where myokine expression dynamically changes and influences systemic health outcomes (Bondi et al.,

AI and network analysis tools is transforming our understanding of skeletal muscle as an endocrine organ. It reveals intricate inter-organ communication pathways and opens new avenues for therapeutic innovation targeting metabolic and degenerative diseases (Gao et al., 2024).

Therapeutic applications in disease

Cancer

AI has been instrumental in elucidating how exercise-induced

myokines such as irisin and oncostatin M modulate the tumor microenvironment. These myokines contribute to vascular normalization, improving blood vessel structure and function within tumors, which can enhance the delivery of therapeutics and reduce hypoxia. Additionally, they play a role in recruiting immune cells to the tumor site, thereby potentially boosting anti-tumor immunity. AI-driven network analyses and machine learning models help identify these complex interactions and predict how myokines influence cancer progression and therapy response, opening avenues for novel immunomodulatory and vascular-targeted cancer treatments (Bondi et al., 2023).

Table 1. Finding the research that relevance to muscle–organ crosstalk & AI.

Research	Key Findings	Relevance to Muscle–Organ Crosstalk & AI
Muscle–Organ Crosstalk: Focus on Immunometabolism (Bay & Pedersen, 2020)	Reviews skeletal muscle as an endocrine organ secreting myokines (e.g., IL-6, irisin) that regulate immunometabolism, energy homeostasis, and inflammation. Exercise-induced myokines counter chronic diseases like obesity and cancer by modulating adipose tissue, liver, and brain function.	Establishes foundational knowledge of myokine networks, critical for AI-driven decoding of muscle–organ interactions. Highlights IL-6's anti-inflammatory role and therapeutic potential.
Muscle–Organ Crosstalk: The Emerging Roles of Myokines (Severinsen & Pedersen, 2020)	Identifies myokines as mediators of exercise benefits in diseases like diabetes, cancer, and neurodegeneration. Discusses their endocrine effects on adipose tissue browning, bone formation, and endothelial function.	Provides a framework for AI applications in mapping myokine pathways and optimizing exercise-based therapies for metabolic and inflammatory disorders.
Muscle–Bone Crosstalk in Chronic Obstructive Pulmonary Disease (Zhang & Sun, 2021)	Explores dysregulation of myokines (e.g., irisin, myostatin) and osteokines (e.g., RANKL) in COPD, linking muscle atrophy and osteoporosis to systemic inflammation. Highlights IL-6 as a biomarker and therapeutic target.	Demonstrates disease-specific muscle–organ crosstalk, offering a model for AI to predict biomarkers or design interventions for comorbidities.
The Transformative Potential of AI in Solid Organ Transplantation (Al Moussawy et al., 2024)	AI enhances donor-recipient matching, predicts graft rejection, and optimizes post-transplant care using machine learning. Applications include automated organ segmentation and mortality prediction models (e.g., OPOM for liver allocation).	Illustrates AI's capacity to analyze complex biological data, a methodology applicable to decoding myokine interactions and predicting therapeutic outcomes.
AI in Rheumatology: Applications in Musculoskeletal Diseases (Cipolletta et al., 2024)	AI aids in diagnosing arthritis, predicting disease progression, and personalizing treatments. Tools analyze imaging (e.g., MRI synovitis quantification) and patient data to optimize biologics and monitor chronic conditions.	Connects AI to musculoskeletal research, relevant for studying myokine-driven inflammation and autoimmune disorders.
Harnessing AI for Human Living Organoid Research (Wang et al., 2024)	AI-driven organoid models simulate in vivo organ interactions, enabling drug screening and disease modeling. Potential to study muscle–organ crosstalk in vitro (e.g., myokine effects on liver or adipose organoids).	Proposes AI-integrated organoids as a platform to validate myokine networks and accelerate preclinical-to-clinical translation.
Muscle-derived extracellular vesicles mediate crosstalk between skeletal muscle and other organs (Jia et al., 2025)	Details how muscle-derived EVs transport myokines (e.g., miR-23a) to organs like the liver and brain, influencing metabolic and inflammatory pathways.	Explores mechanisms of myokine-mediated organ crosstalk, relevant to therapeutic targeting.
Muscle–brain crosstalk mediated by exercise-induced myokines - insights from experimental studies (Kostka et al., 2024)	Identifies BDNF, irisin, and CTSB as BBB-crossing myokines that enhance neurogenesis and synaptic plasticity. Links exercise to neuroprotection in Alzheimer's/Parkinson's models.	Supports AI-driven neurodegeneration therapies via muscle–brain signaling.
Myokines as potential mediators of changes in glucose homeostasis and muscle mass after bariatric surgery (Orioli & Thissen, 2025)	Identifies BDNF, Metn1, and SPARC as key myokines regulating glucose metabolism and muscle mass post-surgery. Highlights their role in obesity and metabolic disorders.	Supports AI-driven discovery of metabolic myokines and their therapeutic potential in obesity/diabetes.
Artificial intelligence in central-peripheral interaction organ crosstalk: the future of drug discovery and clinical trials (Chen et al., 2025)	Demonstrates AI's role in analyzing multi-omics data to model CNS–peripheral organ interactions. Emphasizes biomarker prediction and drug target identification.	Aligns with AI modeling of myokine networks and systemic signaling pathways.
High-resolution analyses of the secretomes from murine C2C12 cells and primary human skeletal muscle cells reveal distinct differences in contraction-regulated myokine secretion (Förster et al., 2025)	Reveals species-specific myokine secretion patterns and identifies 1,440 novel murine myokines. Highlights differences in secretion pathways (ER–Golgi vs. unconventional).	Informs AI-driven myokine discovery and validation challenges in human-specific models.

Metabolic disorders

AI models predict that myokines like brain-derived neurotrophic factor (BDNF) and irisin significantly enhance brain insulin sensitivity and promote the browning of adipose tissue, processes that are critical in combating obesity and diabetes. By improving insulin sensitivity in the brain, these myokines help regulate systemic glucose metabolism, while adipose browning increases energy expenditure. AI techniques integrating multi-omics data and computational modeling facilitate the identification of these myokines as therapeutic targets, enabling precision medicine approaches to metabolic disorders (Diaz-Canestro et al., 2023; Nuriya et al., 2024).

Neurodegeneration

Deep learning approaches have identified key myokines such as cathepsin B (CTSB) and insulin-like growth factor 1 (IGF-1) that can cross the blood-brain barrier and promote neurogenesis and synaptic plasticity. These myokines are implicated in mitigating neurodegenerative processes by supporting neuronal survival, enhancing cognitive function, and potentially delaying the progression of diseases like Alzheimer's and Parkinson's. AI-driven analyses of exercise-induced myokine profiles provide insights into their neuroprotective roles and suggest therapeutic strategies to harness muscle-brain crosstalk for neurodegenera-

-tive disease treatment. In summary, AI-powered methodologies are transforming our understanding of myokine-mediated muscle-organ communication, enabling the discovery of novel therapeutic targets across cancer, metabolic diseases, and neurodegeneration. These advances support the development of myokine-based interventions that leverage exercise biology for disease modification and improved patient outcomes (Gao et al., 2024; Zhang et al., 2022).

Challenges and future directions

Limitations include data heterogeneity and the need for human-specific models. Federated learning and generative AI may address these by synthesizing disparate datasets and predicting myokine interactions in underrepresented populations. Ethical considerations around AI-driven biomarker discovery and personalized exercise prescriptions are also discussed.

Conclusion

The integration of artificial intelligence with myokine research is transforming our understanding of muscle-organ crosstalk by enabling the prediction of novel myokines, modeling complex signaling networks, and identifying therapeutic targets. AI-driven multi-omics and network analysis approaches have provided unprecedented insights into the dynamic regulation of myokines

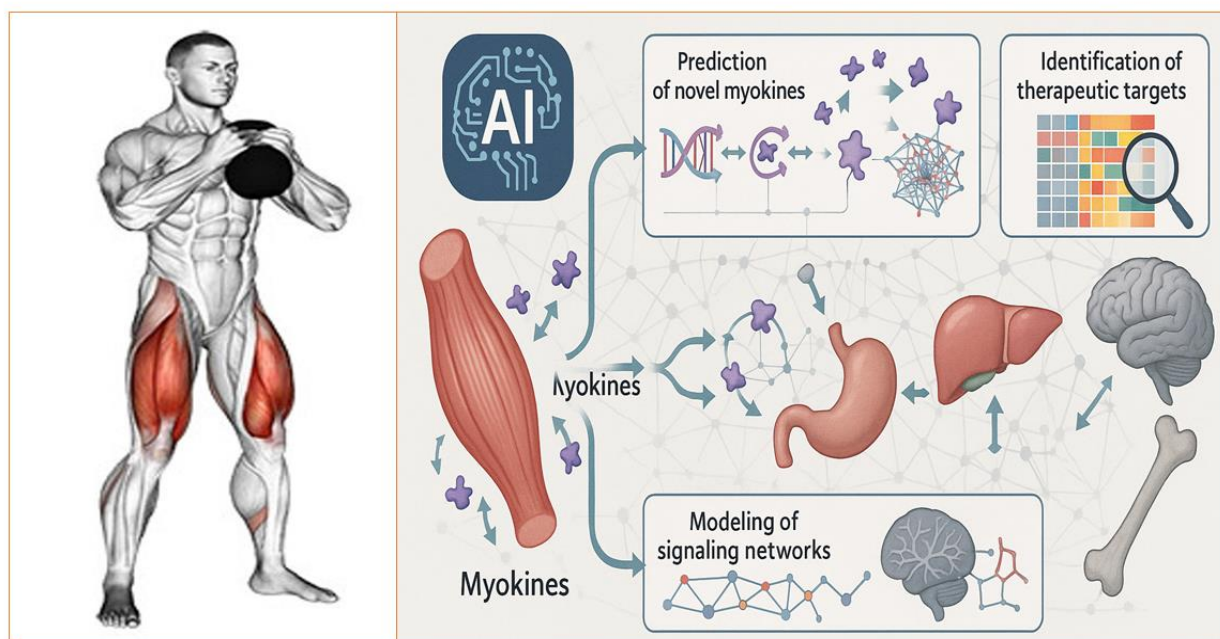


Figure 1. AI decoding myokine interactions.

in health and disease, particularly in exercise-induced contexts and conditions such as obesity, cancer, neurodegeneration, and musculoskeletal aging. These advances highlight the potential of myokines as biomarkers and therapeutic agents, offering new frontiers for personalized medicine. Future research combining AI methodologies with experimental validation will be crucial to fully unravel myokine-mediated communication pathways and translate these findings into clinical interventions that harness muscle-derived signals for systemic health benefits.

What is already known on this subject?

Skeletal muscle functions as an endocrine organ, secreting myokines that mediate crosstalk with organs like the brain, liver, adipose tissue, and vascular system, influencing metabolism, inflammation, and disease progression.

What this study adds?

The integration of artificial intelligence with myokine research is transforming our understanding of muscle–organ crosstalk by enabling the prediction of novel myokines, modeling complex signaling networks, and identifying therapeutic targets.

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