Review

Mechanisms of Exercise-Induced Skeletal Muscle Extracellular Vesicle Secretion and Their Physiological Functions: A Review

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Mechanisms of Exercise-Induced Skeletal Muscle Extracellular Vesicle Secretion and Their Physiological Functions: A Review

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Abstract

The secretion of extracellular vesicles (EVs), particularly exosomes, from skeletal muscle cells is a dynamic and highly regulated process predominantly controlled by intracellular signaling pathways activated during exercise. Physical activity stimulates metabolic and mechanical signals that activate AMP-activated protein kinase (AMPK) and calcium ion (Ca2+) signaling cascades, promoting multivesicular body formation and trafficking, thereby enhancing EV biogenesis and release. The quantity and characteristics of EV secretion vary according to exercise intensity, duration, and modality, with distinct secretion patterns observed between endurance and resistance training. Exercise-induced oxidative stress and mechanical stretch further modulate EV release by altering intracellular redox states and cytoskeletal dynamics. Pharmacological inhibition of EV secretion has revealed their critical role in exercise-induced vascular and systemic adaptations. Moreover, aging and metabolic diseases impair EV biogenesis and secretion, while resistance training can partially restore EV secretion functions in elderly individuals. Collectively, skeletal muscle EV secretion represents a finely tuned outcome of exercise-induced intracellular signaling and mechanical stimuli, serving as a crucial mechanism for systemic communication and adaptation. This review aims to comprehensively summarize the current understanding of the molecular mechanisms underlying exercise-induced skeletal muscle EV secretion and elucidate their physiological roles, highlighting potential therapeutic implications and future research directions in muscle biology and exercise physiology.

Keywords: skeletal muscle; extracellular vesicles; exercise; AMPK; calcium signaling; miRNA; oxidative stress; resistance training; intracellular signaling

Introduction

Skeletal muscle, as the largest metabolic organ in the human body, plays a pivotal role not only in locomotion but also in maintaining systemic metabolic homeostasis. Its remarkable functional adaptability is essential for overall health, influencing energy metabolism, glucose homeostasis, and inter-organ communication. Regular physical exercise is a potent modulator of skeletal muscle physiology, eliciting acute responses and chronic adaptations that significantly reduce the risk of metabolic diseases such as type 2 diabetes and non-alcoholic fatty liver disease [1]. Beyond its mechanical functions, skeletal muscle acts as an endocrine organ, secreting a variety of bioactive molecules, collectively termed myokines, which mediate crosstalk with other tissues including the liver, adipose tissue, pancreas, bone, and cardiovascular system [2]. This secretory function underlies many of the systemic benefits of exercise, as muscle-derived factors influence whole-body metabolism and contribute to the prevention and amelioration of chronic diseases.

Recent research has revealed that skeletal muscle is also a major source of extracellular vesicles (EVs), particularly exosomes, which are nanosized lipid bilayer vesicles encapsulating proteins, lipids, and nucleic acids such as microRNAs (miRNAs). These exosomes serve as critical mediators

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of intercellular communication, facilitating the transfer of molecular signals between muscle cells and distant organs [3][4]. Exercise has been shown to modulate the secretion and molecular cargo of muscle-derived exosomes, thereby influencing physiological processes beyond the muscle tissue itself. For example, exosomes released during or after exercise can carry miRNAs that regulate angiogenesis, inflammation, and metabolic pathways in recipient cells, contributing to vascular health, immune modulation, and metabolic homeostasis [5][6].

The biogenesis and secretion of exosomes in skeletal muscle are tightly regulated by intracellular signaling pathways activated in response to mechanical and metabolic stimuli induced by exercise. Among these, the AMP-activated protein kinase (AMPK) pathway and calcium signaling have emerged as key regulators. AMPK functions as a cellular energy sensor and orchestrates mitochondrial biogenesis, dynamics, and autophagy, processes that are fundamental for muscle adaptation and metabolic health [7]. Activation of AMPK during exercise promotes not only mitochondrial function but also influences the formation and release of exosomes, thereby linking energy metabolism to intercellular communication. Calcium signaling, triggered by muscle contraction, also modulates exosome secretion and cargo composition, integrating mechanical stimuli with molecular signaling networks [8].

Despite advances in understanding the molecular mechanisms governing exosome biogenesis and secretion, the influence of different exercise modalities and parameters—such as intensity, duration, and type (aerobic versus resistance)—on exosome release and function remains incompletely elucidated. Studies indicate that resistance and endurance exercises differentially affect exosomal miRNA profiles and vesicle characteristics, which may underlie distinct physiological adaptations [9][10][9]. Moreover, sex-specific differences in exosome responses to exercise have been reported, suggesting that biological variables further modulate exosome-mediated communication [9]. Understanding these nuances is critical for harnessing the therapeutic potential of muscle-derived exosomes in metabolic and degenerative diseases.

Comprehending the mechanisms of skeletal muscle exosome secretion and their physiological functions is not only fundamental to elucidating the molecular basis of exercise adaptation but also holds promise for identifying novel biomarkers and therapeutic targets. Muscle-derived exosomes participate in regulating systemic metabolism, vascular function, immune responses, and even neuroprotection, highlighting their multifaceted role in health and disease [11][12]. As such, dissecting the regulatory pathways and cargo profiles of exercise-induced exosomes will provide valuable insights into muscle-organ crosstalk and may facilitate the development of exosome-based interventions to mimic or enhance the benefits of physical activity, particularly in populations unable to engage in regular exercise.

2. Main Body

2.1.1. Exercise-Induced Intracellular Signaling Pathway Activation

Exercise acts as a potent physiological stimulus that initiates a cascade of intracellular signaling events in skeletal muscle cells, crucial for the regulation of exosome biogenesis and secretion. One of the primary pathways activated by exercise is the AMP-activated protein kinase (AMPK) pathway, which responds to metabolic stress and mechanical load by promoting energy homeostasis. AMPK activation during exercise is triggered by increases in the AMP/ATP ratio, reflecting the heightened energy demand of contracting muscle fibers. This kinase orchestrates a broad range of metabolic adaptations, including enhanced glucose uptake, fatty acid oxidation, and mitochondrial biogenesis, thereby sustaining cellular energy balance during physical activity [13][14]. Concurrently, calcium (Ca2+) signaling serves as a pivotal mediator of mechanical stimuli in skeletal muscle. Exercise-induced mechanical load elevates intracellular Ca2+ concentrations, which in turn activate various downstream effectors such as calcineurin and Ca2+/calmodulin-dependent protein kinases. These effectors regulate gene expression and protein activity associated with muscle adaptation and vesicular trafficking [15]. Importantly, AMPK and Ca2+ signaling pathways exhibit synergistic

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interactions to fine-tune the expression and activity of proteins involved in exosome biogenesis. For instance, AMPK can modulate the phosphorylation state of key components of the endosomal sorting complex required for transport (ESCRT) machinery, while Ca2+ signaling influences cytoskeletal dynamics essential for vesicle formation [14][16]. The integration of these signaling networks ensures the spatiotemporal specificity of exosome secretion, aligning vesicle release with the metabolic and mechanical demands imposed by exercise. Moreover, redox signaling, mediated by reactive oxygen species generated during muscle contraction, may further modulate these pathways, contributing to the regulation of exosomal cargo sorting and release [17]. Collectively, the dynamic regulation of AMPK and Ca2+-dependent pathways under exercise conditions orchestrates the molecular machinery necessary for the biogenesis and secretion of skeletal muscle-derived exosomes, thereby facilitating intercellular communication and systemic physiological adaptations.

2.1.2. Multivesicular Body Formation and Transport Mechanisms

Multivesicular bodies (MVBs) serve as critical intermediates in the biogenesis of exosomes, originating from the maturation of the endosomal system through intricate membrane remodeling and protein sorting processes. The formation of MVBs relies heavily on the endosomal sorting complex required for transport (ESCRT) machinery, which orchestrates the inward budding of the endosomal limiting membrane to generate intraluminal vesicles (ILVs) that constitute exosomes [18][19]. Exercise influences MVB dynamics by modulating cytoskeletal architecture and motor protein activity, thereby facilitating the directed transport of MVBs toward the plasma membrane for fusion and exosome release. Specifically, exercise-induced mechanical stretch and metabolic stress regulate actin and microtubule networks, enhancing the motility of MVBs along these tracks [16][20]. The membrane fusion event that culminates in exosome secretion involves the coordinated action of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complexes and Rab GTPases, which ensure specificity and efficiency of vesicle docking and fusion [16][20]. Exercise-induced oxidative stress and mechanical forces can alter membrane lipid composition and cytoskeletal stability, thereby modulating the efficiency of MVB trafficking and fusion. For instance, lipid raft domains enriched in ceramides and sphingolipids may facilitate membrane curvature and vesicle budding, processes sensitive to redox state and mechanical tension [21]. Furthermore, the interplay between ESCRT components and the cytoskeleton under exercise conditions ensures the precise spatiotemporal control of exosome release, which is essential for effective intercellular communication during muscle adaptation. Thus, exercise not only stimulates the formation of MVBs but also enhances their transport and fusion with the plasma membrane, optimizing the secretion of bioactive exosomes from skeletal muscle cells.

2.1.3. Composition and Specificity of Skeletal Muscle-Derived Exosomal miRNAs

Skeletal muscle-derived exosomes are enriched with muscle-specific microRNAs (myomiRs), including miR-1, miR-133a, and miR-206, which play pivotal roles in regulating muscle cell proliferation, differentiation, and metabolic adaptation. These myomiRs are selectively packaged into exosomes, reflecting the physiological state and functional demands of the muscle tissue [22][16]. Exercise modulates the expression profile of exosomal miRNAs, with variations observed according to exercise type, intensity, and duration, indicating that exosomal miRNA cargo serves as a dynamic readout of muscle adaptation [23][22]. Functionally, these miRNAs target key signaling pathways such as the Akt1 pathway, which governs muscle hypertrophy and metabolic regulation, thereby influencing muscle remodeling and repair [24][22]. Beyond local muscle effects, emerging evidence suggests that exosomal miRNAs facilitate systemic inter-organ communication, mediating crosstalk between skeletal muscle and distal tissues such as adipose tissue and bone, thus contributing to whole-body metabolic homeostasis [25][26]. For example, miR-146a-5p delivered via muscle-derived exosomes has been shown to inhibit adipogenesis by targeting the GDF5-PPARγ signaling axis in adipose tissue, highlighting the endocrine function of muscle exosomal miRNAs [27]. Moreover, exercise-induced alterations in exosomal miRNA content may enhance angiogenesis and tissue repair

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in ischemic conditions, as demonstrated by hypoxia-modulated miRNAs in skeletal muscle exosomes that promote endothelial cell function [28]. Collectively, the specific composition of skeletal muscle-derived exosomal miRNAs and their modulation by exercise underscore their critical role in muscle physiology and systemic adaptation, positioning them as potential biomarkers and therapeutic targets for muscle-related diseases and metabolic disorders.

2.2. Effects of Exercise Parameters on Skeletal Muscle Exosome Secretion

2.2.1. Regulatory Role of Exercise Intensity and Duration

Exercise intensity and duration are critical determinants of skeletal muscle exosome secretion, modulating both the quantity and molecular composition of these extracellular vesicles. High-intensity exercise has been shown to significantly activate AMP-activated protein kinase (AMPK), a key energy sensor in muscle cells, which in turn promotes an increase in exosome release. AMPK activation facilitates the biogenesis and secretion of exosomes by enhancing multivesicular body (MVB) formation and membrane fusion processes, thus amplifying the export of signaling molecules that mediate systemic adaptations to exercise. Moreover, prolonged endurance training induces a sustained secretion of exosomes, which supports metabolic homeostasis and vascular adaptations necessary for endurance performance. The duration of exercise influences the dynamic changes in exosomal cargo; for instance, longer sessions may alter the profile of microRNAs (miRNAs) and proteins packaged within exosomes, reflecting the evolving metabolic and repair demands of skeletal muscle. Importantly, the temporal pattern of exosome secretion during the recovery phase after exercise mirrors the muscle repair and regeneration processes. This time-dependent release ensures the delivery of bioactive molecules that orchestrate satellite cell activation, inflammation resolution, and extracellular matrix remodeling. Evidence from animal models indicates that exercise duration differentially modulates exosomal miRNA levels, such as miR-27a, which is implicated in metabolic regulation and muscle insulin sensitivity. Specifically, longer exercise bouts reduce circulating exosomal miR-27a levels, which correlates with improved skeletal muscle insulin signaling pathways, highlighting the nuanced role of exercise duration in exosome-mediated metabolic adaptations. Collectively, these findings underscore that both exercise intensity and duration intricately regulate skeletal muscle exosome secretion, shaping their physiological functions in energy metabolism, vascular adaptation, and tissue repair [29] [30].

2.2.2. Differences in Exosome Secretion Patterns Induced by Exercise Types

The type of exercise—resistance versus endurance—exerts distinct influences on skeletal muscle exosome secretion patterns, reflecting divergent adaptive responses at the molecular level. Resistance training primarily activates signaling pathways associated with muscle hypertrophy, such as the mechanistic target of rapamycin (mTOR) pathway, leading to the selective release of exosomes enriched with miRNAs that regulate muscle growth and protein synthesis. These exosomal miRNAs can modulate gene expression in recipient cells, promoting anabolic processes and muscle fiber remodeling. In contrast, endurance training predominantly regulates metabolic adaptations by enhancing mitochondrial biogenesis and angiogenesis. This is mediated through the secretion of exosomes containing miRNAs that target metabolic pathways, such as those involved in oxidative phosphorylation and vascular endothelial growth factor (VEGF) signaling. The quantitative and qualitative differences in exosome secretion between these two exercise modalities are significant; endurance exercise tends to increase the number of exosomes with cargo favoring oxidative metabolism, whereas resistance exercise-derived exosomes carry molecules that support muscle hypertrophy. Notably, combined training modalities may produce synergistic effects, optimizing the exosome-mediated communication network to enhance both metabolic efficiency and muscle growth. This combinatorial approach could potentiate the beneficial systemic effects of exercise by integrating the distinct exosomal signals from resistance and endurance stimuli. The differential exosomal miRNA profiles and secretion rates induced by various exercise types highlight the

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specificity of muscle-derived exosomes as mediators of exercise-induced physiological adaptations [29] [30].

2.2.3. Regulatory Mechanisms of Mechanical Stretch and Oxidative Stress

Mechanical stretch and oxidative stress are pivotal regulators of skeletal muscle exosome secretion, acting through complex intracellular signaling pathways that modulate vesicle biogenesis and cargo loading. Mechanical stretch, a fundamental stimulus during muscle contraction, influences the cytoskeletal tension and facilitates the transport of multivesicular bodies (MVBs) toward the plasma membrane, promoting their fusion and subsequent exosome release. This mechanotransduction process involves the reorganization of actin filaments and activation of focal adhesion kinases, which together enhance exosome secretion in response to mechanical cues. Concurrently, exercise-induced oxidative stress alters the intracellular redox state, impacting the biosynthetic pathways of exosomes. Reactive oxygen species (ROS) generated during muscle activity modulate the activity of redox-sensitive enzymes that are crucial for the sorting of miRNAs and proteins into exosomes. For example, oxidative modifications can influence the loading efficiency of specific miRNAs that regulate antioxidant defenses and metabolic pathways. The interplay between mechanical and oxidative signals forms an intricate regulatory network that ensures the timely and functional secretion of exosomes. This crosstalk enables skeletal muscle cells to adaptively respond to the mechanical load and oxidative environment imposed by exercise, optimizing the release of exosomes that facilitate systemic communication and tissue homeostasis. Understanding these mechanisms provides insight into how skeletal muscle integrates biomechanical and biochemical signals to regulate exosome-mediated intercellular communication during physical activity [29] [30].

2.3.1. Exosome-mediated Muscle-Vascular Communication

Skeletal muscle-derived exosomes serve as critical mediators in muscle-to-vascular communication, particularly in the context of exercise-induced vascular adaptations. These exosomes encapsulate a variety of bioactive molecules, including microRNAs (miRNAs) and proteins, which can be transferred to vascular endothelial cells (ECs) to modulate their function and promote angiogenesis. For instance, exosomal miRNAs such as miR-130a and miR-1, which are enriched in muscle-derived exosomes following exercise, have been shown to enhance endothelial cell proliferation, migration, and tube formation, key processes in new blood vessel formation [31][10]. The underlying mechanisms often involve activation of signaling pathways such as the nuclear factor-kappa B (NF-κB) pathway and reactive oxygen species (ROS) generation, which contribute to endothelial cell activation and angiogenic responses independent of classical vascular endothelial growth factor (VEGF) signaling [31]. Experimental inhibition of exosome release, for example using GW4869, significantly attenuates exercise-induced angiogenesis and improvements in blood flow, underscoring the essential role of exosomes as signaling vectors in this process [32]. Moreover, exosomes facilitate coordinated local and systemic vascular adaptations by delivering muscle-derived signals to distant vascular beds, thereby integrating muscle contraction stimuli with vascular remodeling. This intercellular communication is further supported by evidence that exosomes from vascular smooth muscle cells (VSMCs) and perivascular adipose tissue also participate in endothelial regulation, highlighting a complex network of exosome-mediated crosstalk within the vascular microenvironment [33][34]. Collectively, these findings establish skeletal muscle exosomes as pivotal conveyors of molecular cues that orchestrate vascular endothelial cell function and angiogenesis in response to exercise, thereby contributing to improved vascular health and exercise adaptation.

2.3.2. Role of Exosomes in Systemic Metabolic Regulation

Skeletal muscle-derived exosomes extend their influence beyond local tissue effects to regulate systemic metabolism by targeting distal organs such as the liver and adipose tissue. These exosomes carry specific miRNAs and proteins capable of modulating gene expression networks involved in

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energy metabolism and insulin sensitivity. For example, exercise-induced exosomal miR-136-3p has been identified as a key molecular transducer that enhances glucose uptake and promotes glycolytic metabolism in muscle cells, suggesting a role in fine-tuning systemic glucose homeostasis [35]. Additionally, exosomes derived from skeletal muscle contain miRNAs that regulate lipid metabolism and inflammatory pathways in adipose tissue, thereby influencing whole-body energy balance and metabolic health [36][37]. The transfer of these exosomal miRNAs to hepatic cells modulates lipid metabolism genes, contributing to the amelioration of conditions such as non-alcoholic fatty liver disease (NAFLD) [38]. Furthermore, exosomal cargo can activate key metabolic regulators such as AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) in target tissues, enhancing mitochondrial function and insulin sensitivity [39]. Exercise-induced modulation of exosomal content also promotes metabolic adaptations that counteract obesity and insulin resistance, highlighting their therapeutic potential in metabolic diseases [40][41]. Through these mechanisms, muscle-derived exosomes act as endocrine-like factors, facilitating inter-organ communication that orchestrates systemic metabolic adaptations to exercise and maintains metabolic homeostasis.

2.3.3. Impact of Aging and Metabolic Diseases on Exosome Secretion and Exercise Intervention

Aging and metabolic disorders are associated with impaired exosome biogenesis and secretion from skeletal muscle, which may contribute to diminished muscle adaptability and systemic metabolic dysfunction. Studies indicate that aging leads to a decline in the production and release of muscle-derived exosomes, resulting in reduced delivery of beneficial miRNAs and proteins that support muscle regeneration and metabolic regulation [40][11]. Similarly, metabolic diseases such as type 2 diabetes impair exosomal signaling pathways, exacerbating muscle insulin resistance and vascular dysfunction [9]. Exercise interventions, particularly resistance training, have been shown to partially restore exosome secretion profiles in elderly individuals, enhancing muscle function and metabolic health by re-establishing effective intercellular communication [9][42]. These exercise-induced improvements in exosomal signaling contribute to the attenuation of muscle atrophy and metabolic decline associated with aging. Moreover, exercise modulates the content of exosomes, enriching them with miRNAs and proteins that counteract inflammation and promote anabolic pathways, thereby delaying muscle senescence [4]. Despite these advances, the precise molecular mechanisms by which exercise restores exosome biogenesis and function under pathological conditions remain to be fully elucidated. Future research should focus on delineating the pathways involved in exercise-mediated repair of exosomal signaling in aging and metabolic disease contexts, which may uncover novel therapeutic targets to enhance muscle health and systemic metabolism.

3. Conclusions

In conclusion, the intricate regulation of skeletal muscle-derived exosome secretion represents a pivotal aspect of exercise-induced cellular communication and systemic metabolic adaptation. From an expert perspective, the current body of research underscores that the secretion of these exosomes is not a mere byproduct of muscle contraction but rather a finely tuned process governed by key intracellular signaling pathways such as AMP-activated protein kinase (AMPK) and calcium signaling. These pathways integrate mechanical stimuli and metabolic cues elicited by exercise, orchestrating the release of exosomes that carry specific molecular cargo, including microRNAs (miRNAs), reflective of the muscle's physiological state.

The variability in exercise parameters—intensity, duration, and modality—has been shown to significantly influence both the quantity and molecular composition of muscle-derived exosomes. This variability highlights the complexity of the muscle's adaptive response and suggests that exosomes serve as dynamic messengers tailored to the specific demands imposed by different exercise regimens. Such findings emphasize the necessity of considering exercise heterogeneity in future studies to fully elucidate the functional implications of exosome-mediated signaling.

Importantly, these exosomes facilitate critical inter-organ communication, particularly between skeletal muscle, vascular endothelium, and distal metabolic organs such as the liver and adipose

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tissue. This crosstalk is fundamental to the systemic benefits of exercise, including enhanced metabolic homeostasis and vascular health. The ability of muscle-derived exosomes to modulate target tissues underscores their role as key mediators of exercise adaptation, extending the impact of physical activity beyond the local muscle environment.

The influence of aging and metabolic disease states on exosome function presents both challenges and opportunities. Age-related decline and metabolic dysregulation impair exosome secretion and alter their cargo, potentially diminishing the beneficial effects of exercise-induced signaling. However, evidence suggests that targeted exercise interventions can partially restore exosome functionality, offering promising avenues for therapeutic strategies aimed at mitigating metabolic disorders and age-associated functional decline. This highlights the translational potential of harnessing exosome biology in clinical contexts.

Balancing the diverse research perspectives, it is clear that while significant progress has been made in understanding the role of skeletal muscle-derived exosomes, several gaps remain. The heterogeneity of exosome populations, the complexity of their cargo, and the context-dependent nature of their effects necessitate rigorous, standardized methodologies and integrative approaches combining molecular biology, physiology, and clinical research. Future investigations should prioritize elucidating the precise molecular mechanisms by which exosomes mediate intercellular communication during and after exercise, as well as defining their long-term impact on systemic health.

Moreover, the exploration of exosome-based biomarkers and therapeutic agents holds considerable promise in the fields of exercise medicine and metabolic disease treatment. Advancements in this area could lead to personalized exercise prescriptions and novel interventions that exploit exosome signaling pathways to optimize health outcomes. As such, interdisciplinary collaboration and technological innovation will be critical to translate these foundational insights into practical applications.

In summary, skeletal muscle-derived exosomes constitute a sophisticated communication network integral to exercise-induced physiological adaptations and systemic metabolic regulation. Their modulation by exercise parameters, alteration in pathological states, and potential for therapeutic exploitation position them at the forefront of contemporary research in exercise biology and metabolic health. Continued expert-driven inquiry into their mechanisms and applications will undoubtedly enrich our understanding and enhance clinical strategies aimed at improving human health through physical activity.

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