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Mechanism of exercise-derived circulating exosomes as a target for sarcopenia management

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Sarcopenia, an age-related syndrome characterized by the progressive decline of skeletal muscle mass and function, threatens the health of older adults through underlying mechanisms that include dysregulated protein metabolism, autophagy-mitochondrial dysfunction, chronic inflammation, and impaired regenerative capacity of muscle stem cells. Exercise-derived circulating exosomes, which act as key mediators of intercellular communication, show considerable potential in mitigating sarcopenia-related damage. In this review, we summarize the biogenesis of exercise-induced exosomes, encompassing both ESCRT-dependent and independent pathways, secretion regulated by RAB and SNARE proteins, and their release mediated through mechanical, calcium, metabolic, and neuroendocrine signaling during exercise. We further elaborate on the systemic roles of these exosomes in muscle repair, including alleviating lipotoxicity via the FGF21-adiponectin axis, maintaining protein homeostasis through dual regulation by miR-29c, and ameliorating the inflammatory microenvironment via modulation of macrophage polarization. Finally, we discuss the translational promise of exosomes as therapeutic targets and outline future research directions, offering a conceptual framework for understanding exercise-mediated muscle protection and developing novel interventions.

KEYWORDS

exercise, exosomes, extracellular vesicles, muscle repair, sarcopenia

1 Introduction

1.1 Epidemiological burden of sarcopenia

Defined as age-related loss of skeletal muscle mass and function, sarcopenia leads to functional decline and loss of independence in the elderly (Cruz-Jentoft and Sayer, 2019). Sarcopenia has emerged as a critical global public health issue, severely compromising the quality of life and health status of the elderly. Accumulating epidemiological evidence indicates that the prevalence of sarcopenia increases significantly with age, particularly among individuals with chronic diseases or malnutrition (Morley et al., 2014). Beyond its adverse impacts on physical health, sarcopenia exerts profound negative effects on the quality of life of the elderly population. It is strongly associated with an increased risk of falls, fractures, hospitalization, and premature

death, imposing substantial economic burdens on society and families. Additionally, sarcopenia has been linked to neurodegenerative changes such as brain atrophy, further exacerbating health issues in the elderly. Therefore, early diagnosis and intervention of sarcopenia are crucial for improving the quality of life of the elderly (Alonso-Puyo et al., 2024). However, no specific drugs have been approved for the treatment of sarcopenia to date, making the search for new therapeutic approaches a key research focus (Wen et al., 2025).

1.2 Basic architecture and cellular ecosystem of skeletal muscle

Skeletal muscle, one of the three major muscle tissue types in the human body, is composed of parallel bundles of muscle fibers—the fundamental contractile units. Each muscle fiber contains numerous myofibrils made of actin and myosin filaments, whose formation relies on complex processes of cellular differentiation and fusion (Feng et al., 2020). Muscle function and homeostasis are maintained by a diverse community of resident and infiltrating cells, collectively forming a dynamic cellular ecosystem or niche. The most critical resident muscle stem cells are satellite cells, which reside in a quiescent state between the basal lamina and the sarcolemma—the plasma membrane of the muscle fiber. Upon injury, satellite cells activate, proliferate, and differentiate to drive muscle growth and repair (Feng et al., 2020; Sousa-Vic et al., 2016).

Beyond these, fibroblasts and fibroadipogenic progenitors (FAPs) are responsible for producing and remodeling the extracellular matrix (ECM); in pathological conditions, they can contribute to fibrosis and fat infiltration (Plikus et al., 2021). Endothelial cells form an extensive capillary network essential for nutrient delivery, waste removal, and the provision of angiocrine signals (Rafii et al., 2016). Immune cells, such as macrophages, can adopt an anti-inflammatory, pro-regenerative phenotype to support repair, exhibiting pro-mitotic and anti-apoptotic activities that benefit the survival and growth of myogenic cells (Arnold et al., 2007). Precise communication and coordination among these cellular components are fundamental to muscle adaptation, regeneration, and the maintenance of mass and strength. Consequently, the hallmarks of sarcopenia-including protein loss, metabolic dysfunction, and regenerative failure-can be understood as a disintegration of this finely tuned architectural and cellular harmony under the pressure of aging.

This study aims to explore the potential of exercise as a non-pharmacological intervention in the prevention and treatment of sarcopenia. Exercise is known to confer clear benefits in maintaining and enhancing skeletal muscle function, partly through the regulation of various active factors, including exosomes. As key carriers of intercellular communication, exosomes demonstrate considerable regulatory potential in this context. However, several critical questions remain: How does exercise specifically promote the biosynthesis and secretion of exosomes? And how do exercise-derived exosomes act on skeletal muscle to mitigate sarcopenia-related damage and promote repair? Addressing these questions will deepen our understanding of the molecular basis of exercise-mediated muscle protection. To this end, this review will outline the pathological mechanisms of sarcopenia and synthesize recent advances in the field. It will then focus on analyzing the regulatory pathways through which exercise stimulates exosome release and will examine in detail the mechanisms by which exercise-derived exosomes contribute to injury repair in sarcopenia.

1.3 Pathological mechanisms of sarcopenia

1.3.1 Dynamic imbalance in protein metabolic networks

A core characteristic of sarcopenia is the dynamic imbalance between muscle protein synthesis and degradation, manifested as a combined of anabolic resistance and elevated catabolic activity (Scott et al., 2011). Muscle mass loss occurs when the rate of muscle protein degradation exceeds that of synthesis, which may precede the gradual decline in muscle function (Moore, 2014). During aging, skeletal muscle exhibits a marked reduction in sensitivity to the anabolic response induced by dietary amino acids, with the molecular basis lying in the decreased activation efficiency of the mammalian target of rapamycin complex 1 (mTORC1) pathway (Drummond et al., 2012). Despite elevated phosphorylation levels of certain components of the mTORC1 signaling pathway under basal conditions, the ability of amino acid stimulation to induce mTORC1 nuclear translocation and target gene activation is impaired, leading to reduced ribosome biogenesis and synthesis of actin and myosin. Concurrently, the abnormally activated catabolic program mediated by activating transcription factor 4 (ATF4) upregulates muscle-specific ubiquitin ligases Atrogin-1 (MAFbx) and MuRF1, driving an increased degradation rate of myofibrillar proteins via the ubiquitin-proteasome system (UPS) (Moro et al., 2016).

Age-related inhibition of the insulin-like growth factor 1 (IGF-1)/PI3K/Akt/mTOR pathway further exacerbates anabolic defects. This pathway antagonizes the expression of Atrogin-1/MuRF1 by inhibiting FoxO family transcription factors (e.g., FoxO3a) (Bowen et al., 2015). However, attenuated signaling downstream of the IGF-1 receptor in aged muscle reduces Akt phosphorylation, thereby relieving the inhibition of FoxO3a and forming a vicious cycle of insufficient synthesis and excessive degradation (Wada et al., 2011). Additionally, branched-chain amino acids (BCAAs) play a crucial role in cellular metabolism, particularly in regulating protein synthesis and the mTORC1 signaling pathway. Impaired transmembrane transport efficiency of BCAAs may limit substrate supply for protein synthesis by reducing amino acid-sensing signals in mTORC1, thereby affecting cellular growth and metabolic functions (Lynch and Adams, 2014; Yoshida et al., 2019).

1.3.2 Interactive dysfunction between autophagy-lysosomal system and mitochondria

Dysregulation of autophagic homeostasis is also a key node in the pathological progression of sarcopenia. In aged muscle, the expression of Beclin-1, a core molecule in the macroautophagy pathway, is increased, while the conversion efficiency of LC3-II is significantly reduced. SQSTM1/p62 plays an important role in the fusion of autophagosomes and lysosomes, accompanied by abnormal accumulation of p62/SQSTM1 protein. Its functional defects may lead to impaired degradation of autophagosomes (He et al., 2015; Salazar et al., 2020). This functional impairment

reduces the clearance efficiency of damaged organelles (e.g., mitochondria) and misfolded proteins, leading to elevated levels of reactive oxygen species (ROS) in aged muscle cells, which in turn induce oxidative stress and further inhibit anabolism by oxidatively modifying mTORC1 complex subunits (Goode et al., 2016). Mitochondrial dysfunction and autophagic impairment form a positive feedback loop. A recent study demonstrated that mitochondrial protein homeostasis and fission are altered in aged muscle. Fission and mitophagy are shown to increase with age, while mitochondrial content decreases in both slow and fast muscle fiber types (Murgia et al., 2017).

Mitochondria in aged skeletal muscle exhibit dynamic imbalance, with decreased transcriptional activation efficiency of the mitochondrial biogenesis pathway (PGC-1α/NRF1/TFAM axis), leading to reduced mitochondrial DNA copy number and exacerbating energy metabolism defects, a phenomenon confirmed in various pathological states. Studies have shown that PGC-1α is a key regulator of mitochondrial biogenesis, and its downstream target genes include nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM), which collectively participate in the regulation of mitochondrial DNA replication and transcription (Shen et al., 2014; Chen et al., 2018). Impaired selective clearance capacity of mitophagy, characterized by reduced Parkin-mediated ubiquitination of mitochondria, results in the persistent accumulation of dysfunctional mitochondria. The caspase-3-dependent apoptotic pathway promotes apoptotic loss of muscle fibers, which is a key determinant of age-related muscle loss (Kob et al., 2015).

1.3.3 Chronic inflammation

Chronic low-grade inflammation is recognized as a pivotal driver in the pathogenesis and progression of sarcopenia. Elevated levels of inflammatory factors can promote muscle protein degradation and inhibit protein synthesis (Ogawa et al., 2016). In cancer-related cachexia, inflammatory factors such as IL-6 and TNF-α affect muscle protein metabolism through multiple pathways, leading to muscle atrophy (Feng et al., 2025). Inflammatory responses are the primary mediators of these metabolic alterations, and interventions targeting inflammation may help alleviate the net catabolic effect on muscle protein metabolism (Durham et al., 2009). Furthermore, chronic inflammation promotes muscle atrophy by influencing muscle autophagy and the ubiquitin-proteasome system (UPS), which further emphasizes the central role of inflammation in sarcopenia (Webster et al., 2020). Chronic inflammation can activate pro-inflammatory pathways, such as the NF-κB pathway, which can promote muscle atrophy and adipose tissue expansion. A study on the impact of inflammation on cancer demonstrated that chronic inflammation can induce immune suppression, creating a favorable environment for carcinogenesis (Akkız et al., 2025). Similarly, in sarcopenia, chronic low-grade inflammation may contribute to the development of muscle damage and adipose tissue dysfunction. Another important aspect is the role of hormonal changes. Age-related alterations in the hormonal environment, such as decreased levels of testosterone and growth hormone, can lead to muscle loss and increased adipose tissue accumulation. Insulin resistance, commonly associated with obesity, can disrupt the normal regulation of muscle metabolism, contributing to muscle atrophy. Insufficient nutrient intake, metabolic disorders, hormonal imbalances, and mitochondrial dysfunction are also involved in this process.

1.3.4 Age-related muscle stem cell dysfunction and niche disruption

During the aging process, the homeostasis and function of muscle stem cells (MuSCs) progressively decline. While the total number of MuSCs may decrease with age, a more pivotal change lies in their functional state. Research indicates that aged MuSCs exhibit a diminished capacity for activation, proliferation, and differentiation, which directly undermines the muscle's ability to repair (Cai et al., 2022; Snijders and Parise, 2017; Fry et al., 2015). These intrinsic deficits include metabolic shifts, altered polarity, and epigenetic modifications. For instance, age-related methylation changes can silence genes essential for stem cell self-renewal and quiescence, thereby depleting the regenerative reserve and contributing to sarcopenia progression (Bigot et al., 2015; Chinvattanachot et al., 2024).

Aging induces a profound dysregulation of the overall architecture and signaling networks within the niche. The niche, composed of muscle fibers, endothelial cells, fibroblasts, and immune cells, relies on precise regulation to maintain its function (Li W. et al., 2025). However, a combination of chronic low-grade inflammation, dysregulated extracellular matrix (ECM) composition, impaired vascular support, and a pro-fibrotic shift collectively fosters an inhibitory microenvironment that compromises MuSC function and disrupts intercellular communication (Sousa-Vic et al., 2016; Guillon et al., 2025). Inflammatory cytokines such as IL-1α, IL-13, TNF-α, and IFN-γ present within the inflammatory milieu have been found to stimulate the proliferation of muscle stem cells (MuSCs) and promote their expansion *in vitro* (Fu et al., 2015). This cytokine combination, mediated by inflammation, can rapidly activate MuSCs following muscle injury, promoting their proliferation and differentiation, thereby accelerating the repair process. However, under conditions of chronic inflammation, immune cells such as macrophages may express high levels of transforming growth factor-β1 (TGF-β1). This can inhibit the apoptosis of fibro/adipogenic progenitors, driving their differentiation into matrix-producing cells and consequently promoting fibrosis (Lemos et al., 2015).

Within the aged muscle stem cell microenvironment, increased expression of fibroblast growth factor 2 (Fgf2) leads to the loss of quiescence and self-renewal capacity in a subset of satellite cells (Chakkalakal et al., 2012). Furthermore, intrinsic alterations occur in muscle stem cells during aging, such as increased activity of the p38α and p38β mitogen-activated protein kinase pathways, which further impair their regenerative potential (Cosgrove et al., 2014). Therefore, the impaired regenerative output in sarcopenia is best understood as the downstream result of a degenerative cycle: aging erodes the functional competence of MuSCs and corrupts their regulatory niche, which together lead to a failure in mounting effective repair responses.

The pathological mechanisms of sarcopenia form a multi-layered and intricately interconnected network, with its core lying in the systemic homeostatic imbalance induced by aging. This imbalance is specifically manifested as: a dynamic imbalance in the protein metabolic network; dysfunction of the autophagy-mitochondrial axis, where impaired autophagic flux and decreased

mitochondrial biogenesis create a vicious cycle; chronic low-grade inflammation, which promotes protein degradation and inhibits synthesis; and the functional exhaustion of muscle stem cells coupled with microenvironment dysregulation. These mechanisms do not exist in isolation but rather interact and influence each other, collectively forming a vicious cycle characterized by reduced synthesis, increased breakdown, failed clearance, and ineffective repair. Ultimately, this leads to the progressive loss of skeletal muscle mass and function.

2 Biogenesis of exercise-induced circulating exosomes

2.1 Basic characteristics of exosomes

Exosomes are nanoscale extracellular vesicles secreted by virtually all cell types, possessing unique biological properties. They typically have a diameter ranging from 30 to 140 nm and a lipid bilayer membrane structure, and are a key subclass of extracellular vesicles (Safdar and Tarnopolsky, 2018). Extracellular vesicles are small membrane-enclosed vesicles that originate from multivesicular bodies or the plasma membrane. Virtually all cell types release extracellular vesicles, which are present in a wide range of bodily fluids such as blood and milk. Their biogenesis occurs primarily through two pathways: one involves direct outward budding or shedding of the plasma membrane to generate larger microvesicles, while the other entails inward budding of the membrane of intracellular multivesicular bodies to form intraluminal vesicles; subsequent fusion of these multivesicular bodies with the plasma membrane releases the intraluminal vesicles into the extracellular space as nanoscale exosomes (Pegtel and Gould, 2019; Robbins and Morelli, 2014).

Their molecular composition is highly complex and functionally diverse, comprising three major classes of biomolecules: lipids, proteins, and nucleic acids (Isaac et al., 2021). Lipids are characterized by phosphatidylserine enriched in the outer membrane, cholesterol that maintains membrane stability, sphingomyelin involved in signal transduction, and ceramide that drives ESCRT-independent biogenesis (Nail et al., 2023). Proteins include structural proteins (e.g., cytoskeletal proteins, membrane - binding proteins); functional proteins (HSP70/HSP90, Rab5/7, integrins); signature proteins (Tetraspanins CD63/CD81/CD9), and transferrin receptor (Fan et al., 2023). Nucleic acids carry genetic information substances such as mitochondrial DNA (mtDNA), translatable mRNAs, and regulatory non-coding RNAs (ncRNAs, lncRNAs, and circRNAs) (Jung et al., 2025).

Exosomes and their biogenesis process play an important role in maintaining protein quality, as their release can trigger the reorganization of the surrounding extracellular matrix and facilitate intercellular communication. Once secreted, exosomes can enter the interstitial space and eventually the circulatory system, exerting effects in local paracrine or distal systemic pathways. They are key components of intercellular and interorgan communication systems, capable of carrying biological signals from 1 cell type or tissue to another (Jørgensen et al., 2013). In metabolic processes, exosomes regulate metabolic pathways in target cells by transferring bioactive molecules such as miRNAs, participating in the pathogenesis and progression of metabolic diseases (Cunha et al., 2024) (Figure 1, by figdraw.com).

2.2 Molecular mechanisms of exosome biogenesis

The biogenesis of exosomes proceeds through a highly regulated cascade, encompassing the invagination of the plasma membrane to form early endosomes, the invagination of multivesicular bodies (MVB) to generate intraluminal vesicles (ILV), and the fusion of MVB with the plasma membrane for exosome release. Its molecular mechanisms involve two core pathways: ESCRT-dependent and ESCRT-independent (Wei et al., 2021; Yanagawa et al., 2024). Exosome biogenesis initiates with the invagination of the plasma membrane to form endosomes, and the endosomal membrane further buds inward to generate MVB containing ILV. In the ESCRT-dependent pathway, the classical regulatory mechanism relies on ESCRT complexes (ESCRT-0, -I, -II, -III) coordinated with ubiquitination-based sorting mechanisms. These complexes mediate the recognition and enrichment of membrane-bound cargo, and drive the invagination of the MVB membrane. ESCRT complexes play a pivotal role in MVB biogenesis: ESCRT-0 is responsible for recognizing and clustering ubiquitinated cargo, ESCRT-I and ESCRT-II function in the inward budding of the membrane, and ESCRT-III mediates membrane scission to complete ILV formation. These vesicles then transport the cargo to lysosomes for degradation (Wollert and Hurley, 2010). In contrast, the ESCRT-independent pathway relies on adaptor molecules such as tetraspanins and Syntenin-ALIX, and mediates the invagination of the MVB membrane to form ILV through the synergistic action of lipid microdomains and protein complexes (Bissig and Gruenberg, 2014). The two pathways differ in their focus on cargo sorting and the regulation of membrane dynamics (Colombo et al., 2014).

MVB have two fates after formation: some fuse with lysosomes, and their contents are degraded; others proceed to the secretory pathway, and ILV are released into the extracellular space through fusion with the plasma membrane. If these released ILVs also meet the established size criteria for exosomes (30–140 nm), they are defined as exosomes; otherwise, they are more broadly classified as EVs. ILV are the precursor structures of exosomes, and they are enriched with bioactive molecules (such as RNA and proteins) derived from donor cells. Moreover, the composition of these components differs significantly from that of the parent cells, which stems from the specific cargo sorting mechanism during MVB formation (Kalluri and LeBleu, 2020).

Exosomes stably contain characteristic markers such as tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP60, HSP70), and ESCRT-related components (Alix, TSG101) (Théry et al., 2002; Regimbeau et al., 2022; Simons and Raposo, 2009; Li W. et al., 2017), providing a molecular basis for their identification. The secretion process of exosomes mainly depends on the synergistic action of RAB family small GTPases and SNARE family proteins. RAB proteins (e.g., RAB11, RAB35, RAB27A/B) regulate the transport, localization, and docking of MVB with the plasma membrane through interaction with the cytoskeleton (Savina et al., 2005; H et al., 2010). SNARE complexes (e.g., VAMP7,

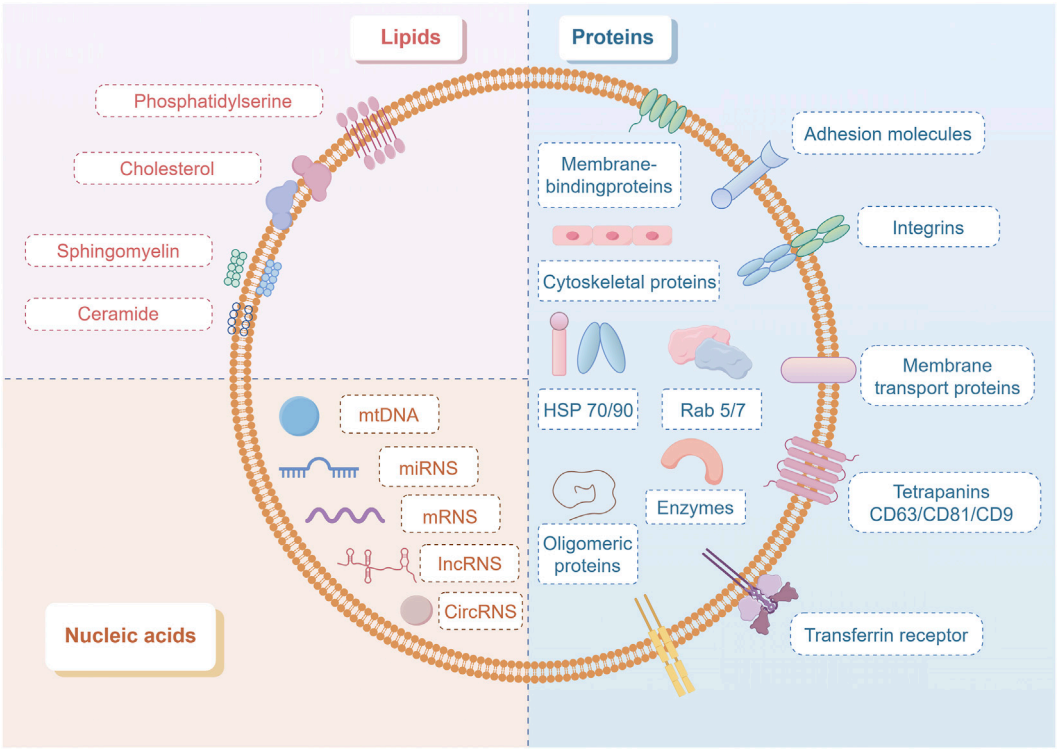

FIGURE 1
Schematic diagram of exosomal molecular composition.

YKT6, etc.) promote the fusion of MVB with the plasma membrane and the final release of exosomes by mediating membrane fusion (Gross et al., 2012; Zylbersztejn and Galli, 2011) (Figure 2).

2.3 Exercise-induced biogenesis of exosomes

Exercise can induce the rapid release of exosomes. Evidence indicates that in healthy individuals, after exhaustive exercise such as cycling or running, exercise significantly increases nanoscale exosomes in the blood, and exosome release begins early in exercise, even before the individual reaches the anaerobic threshold. In a study involving healthy individuals undergoing incremental cycling exercise, it was found that small extracellular vesicles with exosome-characteristic sizes and carrying exosome-specific proteins in plasma increased significantly immediately after exercise, and returned to pre-exercise levels after 90 min of rest (Frühbeis et al., 2015). In a study involving nine healthy young men, venous blood samples were collected before, during, and throughout the recovery period of a 1-h moderate-intensity (or high-intensity) semi-recumbent cycling exercise and a time-matched rest control trial. Platelet-derived exosomes increased from baseline only during high-intensity exercise. During exercise, platelet microvesicles (PMV) were correlated with brachial artery shear rate and plasma norepinephrine concentration; compared with resting exosomes, exercise-derived exosomes enhanced endothelial cell proliferation, migration, and tube formation (Wilhelm et al., 2016). These results indicate that high-intensity exercise leads to a substantial increase in circulating PMV, which may play a role in exercise-mediated vascular healing and adaptation. As a type of extracellular vesicle, exosomes play a key role in intercellular communication, serving as important carriers for intercellular information transmission and capable of regulating cellular physiological functions and phenotypes (Zylbersztejn and Galli, 2011).

Exercise-induced circulating exosomes have a complex and diverse composition, containing multiple biomolecules that play important roles in intercellular communication and physiological regulation. Proteins are key components of exosomes; exosomes from different sources have specific protein profiles involved in various cellular physiological processes such as signal transduction and metabolic regulation. In plasma exosomes from patients with primary biliary cirrhosis, proteins related to immune regulation can be detected, which can modulate the expression of co-stimulatory molecules in monocyte populations and influence immune responses (Tomiyama et al., 2017). Exosomes trigger biological changes in recipient cells by delivering their carried bioactive substances such as proteins and nucleic acids. In metabolic diseases, exosomes secreted by adipocytes can carry miRNAs related to lipid metabolism and transfer them to liver or skeletal muscle cells, regulating lipid metabolism processes in these cells (Li W. et al., 2017).

Exosomes are rich in nucleic acids, including miRNAs, mRNAs, and mitochondrial DNA. miRNAs are particularly important in exercise-induced circulating exosomes, as they can regulate target gene expression and participate in cellular processes such

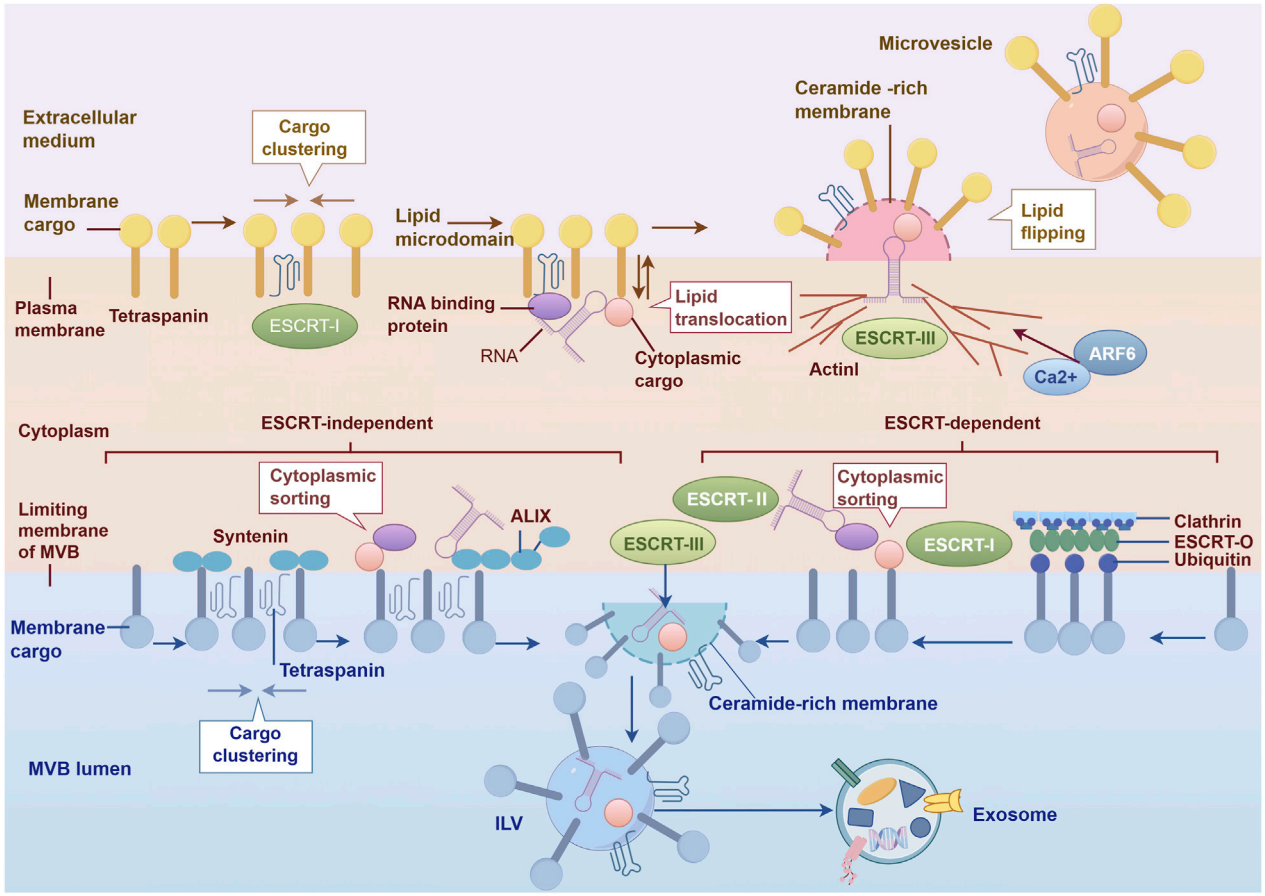

FIGURE 2
Schematic diagram of the molecular mechanism of exosome biogenesis.

as proliferation, differentiation, and apoptosis. Studies have found that the expression levels of certain miRNAs in circulating exosomes change significantly after exercise, such as miR-21 and miR-26, which may be related to exercise-induced physiological adaptation and tissue repair (Karvinen et al., 2020). Multiple muscle-related microRNAs (miRNAs) are upregulated in circulating exosomes after exercise, including but not limited to miR-1, miR-133a/b, miR-206, miR-208a, and miR-499 (Castaño et al., 2020; Vechetti et al., 2021; Annibalini et al., 2019; D'Souza et al., 2018). These changes have been reported after both short-term and long-term exercise interventions. Importantly, various exercise modalities have been confirmed to induce an increase in the total number of exosomes in the blood, especially subpopulations of exosomes enriched with miRNAs (Gomes et al., 2014; Kawanishi et al., 2023). Although this research field is relatively new, studies have explored the impact of acute exercise on specific exosome subtypes through detailed analysis of exosomal surface markers and their carried gene expression profiles, revealing that exercise significantly regulates the expression of exosomal surface markers. Exosomes are also involved in immune regulation and inflammatory responses. In immune responses, exosomes secreted by immune cells can regulate the activity of other immune cells, influencing the intensity and direction of immune responses: exosomes from dendritic cells can activate T cells to enhance immune responses, while exosomes from regulatory T cells have immunosuppressive effects, inhibiting excessive immune reactions (Agarwal et al., 2014).

Exercise triggers the release of circulating exosomes through multi-level physiological stimuli, with core mechanisms involving the synergistic action of mechanical signal transduction, calcium ion oscillations, energy stress responses, and neuroendocrine regulation (Whitham et al., 2018). These pathways interact synergistically to regulate exosome biogenesis and secretion, with calcium signaling acting as a central hub. The rapid release of exosomes during exercise may also be triggered by multiple exercise-related physical and biochemical signals. Initial stimuli may originate from direct mechanical signals such as blood flow shear stress and muscle contraction itself (Hou et al., 2019; Obi et al., 2025). Exercise may regulate the formation and secretion of exosomes by affecting intracellular calcium ion concentration and protein kinase activity, and may also influence intracellular membrane transport systems, promoting the fusion of multivesicular bodies with the cell membrane to release exosomes into the extracellular environment (Vechetti et al., 2021). In skeletal muscle, action potentials induced by motor neurons trigger the massive release of Ca^{2+} from the sarcoplasmic reticulum; these Ca^{2+} not only

participate in excitation-contraction coupling but may also promote exosome release more rapidly than in other tissues (Whitlock and Hartzell, 2017). Exercise triggers intracellular Ca^{2+} oscillations through mechanical stress (e.g., Piezo1 activation) and metabolic stress (AMPK/mTORC1 pathway) (Zhang et al., 2021), which in turn activate calmodulin and SNARE complexes (Zhang et al., 2021; Amemiya et al., 2021), ultimately driving MVB anchoring and fusion with the plasma membrane (Ohya et al., 2024). When plasma membrane receptors are activated, integrins sense deformation of the extracellular matrix and promote endosome formation through the FAK/PI3K signaling pathway; meanwhile, the Piezo1 ion channel responds to membrane changes, mediating Ca^{2+} influx and driving MVB transport (Li et al., 2014). Ca^{2+} plays a core regulatory role in exercise-promoted exosome release: during exercise, motor neurons generate action potentials, prompting the opening of sarcoplasmic reticulum RyR channels and a transient increase in cytoplasmic Ca^{2+} concentration (Savina et al., 2003); Ca^{2+} activates Rab GTPases (Rab27a/Rab35) through calmodulin, promoting MVB anchoring to the plasma membrane (Ostrowski et al., 2010); Synaptotagmin-7 mediates the assembly of SNARE complexes (VAMP7/STX4) to initiate membrane fusion (Fader et al., 2009).

Energy consumption during exercise can promote AMPK activation, during which phosphorylated Raptor inhibits mTORC1, thereby relieving inhibition of ULK1 and activating autophagy-related MVB formation (Saikia and Joseph, 2021). Reactive oxygen species (ROS) also increase transiently, promoting HIF-1α stabilization and upregulating the Syntenin-Alix pathway, which regulates exosome biogenesis and release through an ESCRT-independent pathway (King et al., 2012). Concurrently with elevated ROS, catecholamine hormones (epinephrine and norepinephrine) increase, activating the PKA signaling pathway through β2-AR receptors and phosphorylating Rab8A to enhance exosome secretion (Singh and Moniri, 2012; Rambacher and Moniri, 2020). Increased cortisol promotes GR receptor-mediated upregulation of CD63 and HSP90 expression, facilitating exosome release (Whitham et al., 2018) (Figure 3).

Regarding the cellular sources of exercise-induced exosomes, existing evidence indicates their heterogeneity. Flow cytometry or immunocapture analyses have shown that these exosomes are primarily derived from lymphocytes ($CD4^+$, $CD8^+$), monocytes ($CD14^+$), endothelial cells ($CD105^+$, $CD146^+$), and platelets ($CD41^+$) (Brahmer et al., 2019; Bocchetti et al., 2024; Burrello et al., 2022) (Table 1). Skeletal muscle tissue has also been identified as a contributor, which can be characterized by the specific marker α-sarcoglycan ($SGCA^+$). Even low-intensity exercise is sufficient to stimulate exosome secretion, and the release of exosomes tends to increase with the prolongation of exercise duration or the enhancement of exercise intensity (Gomes et al., 2017). The release intensity of skeletal muscle-specific exosomes ($SGCA^+$) is positively correlated with exercise duration and intensity (Hoffman et al., 2025). However, the exact function of skeletal muscle-derived exosomes in exercise physiological responses remains insufficiently understood. Although skeletal muscle is known to release various factors (such as myokines) during exercise, its relative contribution to the total pool of circulating exosomes observed after exercise has not been clarified. Current viewpoints tend to suggest that exosome release during exercise is the result of multiple cell types (immune cells, endothelial cells, platelets, and muscle cells) collectively responding to exercise stimuli.

While exercise is a potent stimulus for exosome release, determining the precise tissue of origin for circulating exosomes remains a significant challenge. Although skeletal muscle is a major secretory organ during physical activity, the systemic nature of exercise involves simultaneous metabolic flux in the liver, adipose tissue, endothelial cells, and the immune system (Fan et al., 2021; Saçma and Geiger, 2021). Consequently, the exercise-induced exosome pool is highly heterogeneous, likely containing vesicles from all these tissues rather than muscle alone. Furthermore, the fate of these vesicles—whether they are 'targeted' to specific acceptor tissues via surface ligand-receptor interactions or simply distributed stochastically via circulation remains under investigation. Recent evidence supports a degree of organotropism, such as the preferential uptake of muscle-derived exosomes by the liver, yet, likely, a substantial portion of these vesicles are widely distributed or cleared by the reticuloendothelial system (Whitham et al., 2018). Thus, exercise-induced exosomes should be viewed as a systemic signaling network rather than a purely myokine-like phenomenon.

3 Systemic roles of exercise-induced circulating exosomes in muscle repair

3.1 Alleviating lipotoxicity

Exosomes play a significant role in mitigating lipotoxicity, thereby helping to maintain normal myocyte function. Lipotoxicity refers to the phenomenon in which excessive intracellular lipid accumulation leads to cellular dysfunction and damage. In the context of sarcopenia, age-related metabolic disorders often cause ectopic lipid deposition in skeletal muscle, which significantly impairs metabolic function, exacerbates insulin resistance, and promotes muscle mass loss (Bosma et al., 2012; Borén et al., 2013). In individuals with obesity and type 2 diabetes, lipotoxicity not only contributes to insulin resistance but may also directly drive muscle atrophy (Meex et al., 2019). Therefore, targeting lipotoxicity represents an important strategy for delaying the progression of sarcopenia.

Research demonstrates that exosomes derived from mesenchymal stem cells can regulate lipid metabolism by activating the FGF21-adiponectin axis: exosomes inhibit skeletal muscle lipoprotein lipase (LPL) activity via the ANGPTL4 protein, while simultaneously activating the hepatic miR-122-5p/Keap1/Nrf2 axis to promote FGF21 synthesis, thereby driving systemic fatty acid oxidation (accompanied by increased CPT1a expression) (Kim et al., 2024). This regulatory mechanism alleviates high-fat-diet-induced hepatic steatosis and insulin resistance in obese mice, consequently reducing lipid-mediated toxicity to muscle cells (Kim et al., 2024). From the perspective of sarcopenia, activation of this pathway may help improve metabolic flexibility in aged muscle, attenuating the negative impact of lipid accumulation on contractile function and protein synthesis.

Specifically, exosomes may alleviate lipotoxicity through multiple mechanisms. On one hand, exosomes can modulate the expression of lipid-metabolism-related genes, promoting fatty acid oxidation and reducing intracellular lipid accumulation. For

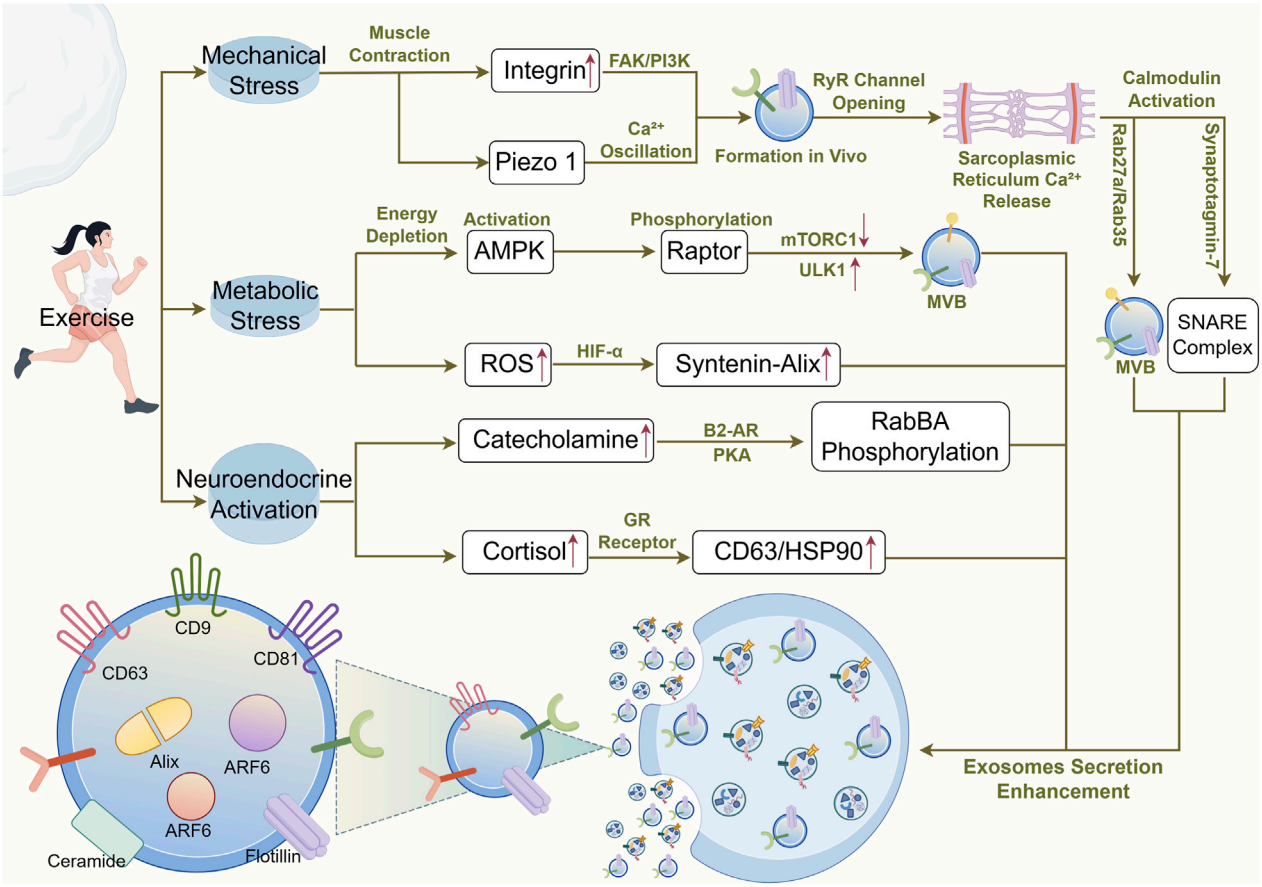

FIGURE 3
Schematic diagram of the mechanism underlying exercise-induced exosome secretion.

example, in primary grass carp hepatocytes, exosomes derived from fatty hepatocytes enrich glucose-regulated protein 78 (GRP78) to activate inositol-requiring enzyme-1α (IRE1α), thereby promoting lipid accumulation; conversely, inhibiting the GRP78 or IRE1α pathway reduces lipid accumulation, highlighting the regulatory role of exosomes in lipid metabolism (Yang et al., 2024). On the other hand, exosomes can mitigate inflammation-induced damage caused by lipotoxicity by modulating inflammatory responses. For instance, macrophage-derived exosomes protect bone in an osteoporotic mouse model by delivering miR-3102-5p, which suppresses lipid peroxidation and inflammatory responses, thereby indirectly alleviating the impact of lipotoxicity on the musculoskeletal system (Geng et al., 2024) (Table 2). These anti-inflammatory and metabolic regulatory effects suggest that exercise-derived exosomes may, through similar pathways, counteract chronic low-grade inflammation and disordered lipid metabolism in aging individuals, thereby protecting muscle from lipotoxic damage.

Exercise can counteract lipotoxicity by improving lipid turnover and lipid droplet quality. Within the pathological context of sarcopenia, aging muscle frequently exhibits disordered lipid metabolism and ectopic lipid deposition, which exacerbates insulin resistance and muscle loss; therefore, exercise intervention targeting lipotoxicity is of significant importance for delaying sarcopenia. In a review focusing on the latest human data, it was found that lipotoxicity is typically characterized by an increase in bioactive lipid species such as ceramides. For example, in obese individuals, exercise training reduces intramuscular ceramide content without necessarily decreasing ectopic lipid storage. Evidence also indicates that exercise training elevates markers of lipid droplet dynamics, including PLIN proteins, triglyceride lipases ATGL and HSL, as well as mitochondrial efficiency. This may explain the improved lipid turnover and reduced accumulation of lipotoxic intermediate products observed in athletes, despite their increased intramuscular lipid levels (Zacharewicz et al., 2018). These findings suggest that exercise likely protects aged muscle from lipotoxic damage by optimizing the balance between lipid storage and utilization, thereby helping to preserve muscle mass and function-offering a mechanistic rationale for exercise in the prevention and management of sarcopenia.

In a study on the cardioprotective mechanism of Turbo cornutus, oxidative damage was induced in freshly isolated hearts by incubation with 0.1 mM $FeSO_4$ *in vitro*. Treatments were performed by co-incubation with Turbo cornutus extract or gallic acid (as a standard antioxidant). The induction of oxidative cardiac damage led to significant changes in lipid-related parameters, such as depletion of glutathione, triglycerides,

TABLE 1 Cellular sources and functional characteristics of exercise-induced exosomes.

Cellular source	Key molecular markers	Core biological functions	Regulatory mechanisms
Platelets	$CD41^+$, P-selectin	Promote angiogenesis, enhance endothelial repair, and improve endothelial cell proliferation, migration, and tube formation capacity	Respond to blood flow shear stress, activate the FAK/PI3K pathway via β-integrins; catecholamine-PKA-Rab8A axis promotes release (Wilhelm et al., 2016; Zhang et al., 2021)
Skeletal muscle cells	$SGCA^+$, α-sarcoglycan, miR-206	Facilitate muscle regeneration and repair, activate satellite cells, and inhibit MuRF1/Atrogin-1 expression	Muscle contraction induces Ca^{2+}-PKC pathway activation; ROS-HIF-1α upregulates the Syntenin-Alix pathway (King et al., 2012)
Endothelial cells	$CD146^+$, eNOS	Maintain vascular homeostasis, improve endothelial function, and enhance NO-mediated vasodilation and anti-inflammatory effects	Laminar shear stress activates the Piezo1-Ca^{2+} channel; AMPK/mTORC1-ULK1 pathway drives MVB formation (Whitham et al., 2018; Zhang et al., 2021; Saikia and Joseph, 2021)
Immune cells	$CD14^+$, $CD4^+$, $CD8^+$	Regulate the inflammatory microenvironment, promote M2 macrophage polarization, and inhibit excessive immune responses	Cortisol-GR receptor upregulates CD63/HSP90; catecholamines enhance exosomal immunomodulatory functions via β_2-AR (Agarwal et al., 2014; Whitham et al., 2018)
Other cells	HSP70/90, Tetraspanins	Systemic metabolic regulation, modulate lipid oxidation, and improve insulin sensitivity	Synergistic action of metabolic stress-induced AMPK activation, Ca^{2+}, and the Synaptotagmin-7-SNARE axis (Amemiya et al., 2021; Ohya et al., 2024; Saikia and Joseph, 2021)

Abbreviations: *$SGCA^+$*, α-sarcoglycan positive; *PKA*, Protein Kinase A; *Rab8A*, Ras-related protein Rab-8A; *Ca^{2+}-PKC*, Calcium Ion-Protein Kinase C; *ROS*, reactive oxygen species; *HIF-1α*, Hypoxia-Inducible Factor 1α; *NO*, nitric oxide; *GR*, glucocorticoid receptor; *HSP90*, Heat Shock Protein 90; *β_2-AR*, β_2-Adrenergic Receptor; *HSP70*, Heat Shock Protein 70.

HDL-cholesterol, superoxide, catalase, and ENTPDase activity levels, while increasing malondialdehyde, cholesterol, LDL-cholesterol, ACE, acetylcholinesterase, ATPase, and lipase activity levels. These levels and activities were significantly reversed after Turbo cornutus treatment, indicating its ability to alleviate lipotoxicity and regulate dysregulated cardiac metabolic activities (Erukainure et al., 2021). Although this study focused on cardiac tissue, its demonstrated mechanisms of modulating lipid metabolism and oxidative stress provide a valuable reference for understanding how exercise-derived exosomes might mitigate lipotoxicity in aged muscle. In sarcopenia, exercise may, through the induced release of exosomes with analogous regulatory functions, indirectly help improve the lipid metabolic state of muscle, thereby counteracting age-related muscle loss.

3.2 Maintaining muscle protein homeostasis

Exercise-derived exosomes carrying miR-29c play a key role in maintaining muscle protein homeostasis, with critical importance for counteracting the pathological core of net protein loss in sarcopenia (Silva et al., 2019). Through a dual regulatory mechanism, miR-29c coordinately balances muscle protein synthesis and catabolism-directly addressing the two major defects in sarcopenia: excessive catabolism and insufficient anabolism (Silva et al., 2019; Alves et al., 2022; Xie et al., 2021). On one hand, miR-29c directly inhibits the expression of muscle-atrophy-related ubiquitin ligases TRIM63/MuRF1 and FBXO32/atrogin-1, thereby reducing muscle protein degradation. On the other hand, it promotes the proliferation and differentiation of satellite cells, enhancing muscle protein synthesis. During aging, the decline in satellite-cell function and the exacerbation of anabolic resistance make this dual regulation particularly crucial in the context of sarcopenia (Silva et al., 2019; Li J. et al., 2017).

This dual action has been validated in cellular and animal models: in C2C12 myoblast experiments, miR-29c oligonucleotide treatment enhanced cell differentiation, as reflected by increased immunostaining of myocyte enhancer factor-2 (MEF2), elevated myotube fusion index, and upregulated mRNA levels of myogenesis-related markers (Wu et al., 2025). *In vivo*, overexpression of miR-29c increased the mass of the tibialis anterior muscle, accompanied by greater fiber cross-sectional area and strength (Wu et al., 2025). Notably, in a mouse model of muscle atrophy induced by unilateral ureteral obstruction (UUO), injection of exosomes carrying miR-29c increased myofiber cross-sectional area and reduced the expression of the aforementioned atrophy-related factors, thereby ameliorating muscle wasting (Wang et al., 2019). These results not only confirm the function of miR-29c but also suggest the

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TABLE 2 Effects of exercise on exosome biogenesis.

Author	Experimental model	Age	Intervention protocol	Model type	Sample type	Post-exercise outcomes	Core molecular mechanisms
Whitham et al. (2018)	Healthy humans	27 ± 1 years old	1-h acute cycling exercise	Human trial	Circulating EV	Increased release of over 300 EV-associated proteins	EV-carried proteins accumulate in the liver, drive inter-tissue communication, and activate fatty acid oxidation
Kim et al. (2024)	High-fat diet-induced obese mice	19 weeks old	Mesenchymal stem cell-derived exosome intervention	Animal model	Liver/skeletal muscle	Reduced hepatic steatosis, improved insulin sensitivity	Activated FGF21-adiponectin axis; ANGPTL4 reduced LPL activity by 72%; miR-122-5p/Keap1/Nrf2 increased FGF21 (3.8-fold); enhanced fatty acid oxidation (CPT1a upregulation)
Sullivan et al. (2022)	Obese mice	18–35 weeks old	7-day combined aerobic + resistance exercise	Animal model	Skeletal muscle small EV	Altered miRNA profiles targeting inflammation/growth pathways	Regulated Wnt/β-catenin, PI3K/AKT, IGF-1, PTEN, PEDF pathways; reduced Jun, Fos, and IL-8 mRNA
Oliveira et al. (2018)	Healthy rats	Not reported	Acute aerobic exercise	Animal model	Serum EV	Changes in EV diameter, concentration, and small RNA content	Exercise intensity-dependent mechanism of EV release
Lovett et al. (2018)	Muscle injury model	18–30 years old	Two bouts of muscle-damaging exercise	Human trial	Circulating EV	Dynamic changes in muscle-specific miRNAs	miR-206, miR-133, etc., involved in muscle repair
Barone et al. (2016)	Healthy rats	Not reported	Endurance training	Animal model	Skeletal muscle tissue	Increased expression of heat shock protein HSP60	HSP60 induced PPARγ coactivator expression, promoting metabolic adaptation
Rigamonti et al. (2020)	Healthy obese population	12.4–36.5 years old	Acute exercise	Human trial	Circulating EV	EV count regulated by BMI and gender	Mechanisms underlying tissue-specific differences in EV release

(Continued on the following page)

TABLE 2 (*Continued*) Effects of exercise on exosome biogenesis.

Author	Experimental model	Age	Intervention protocol	Model type	Sample type	Post-exercise outcomes	Core molecular mechanisms
Wang et al. (2019)	Muscle atrophy model mice	8 weeks old	miR-29c exosome injection	Animal model	Skeletal muscle	Increased myofiber cross-sectional area, reduced atrophy factors	Dual regulation by miR-29c: decreased TRIM63 (MuRF1)/FBXO32 (atrogin-1); enhanced satellite cell proliferation and differentiation
Li et al. (2025b)	Tendinopathy	Not reported	Tendon stem cell exosomes + ECM hydrogel	Animal model	Tendon tissue	Enhanced tendon regeneration, reduced inflammatory infiltration	Promoted M2 macrophage polarization; decreased TNF-α/IL-1β
Chen et al. (2018)	Osteoarthritis	Not reported	IL-1β-pretreated HucMSCs exosomes	Cell model	Chondrocytes/ macrophages	Increased cartilage matrix production, promoted M2 macrophage polarization	miRNA regulated inflammatory pathways; decreased pro-inflammatory factors, improved anti-inflammatory microenvironment

Abbreviations: *Ev*, Extracellular Vesicles; *FGF21*, Fibroblast Growth Factor 21; *ANGPTL4*, Angiopoietin-like Protein 4; *LPL*, lipoprotein lipase; *miR-122-5p*, MicroRNA-122-5p; *Nrf2*, Nuclear Factor Erythroid 2; *CPT1a*, Carnitine Palmitoyltransferase 1a; *IGF-1*, Insulin-like Growth Factor 1; *PTEN*, phosphatase and tensin homolog; *PEDF*, Pigment Epithelium-Derived Factor; *IL-8*, Interleukin-8; *mRNA*, Messenger RNA; *HSP60*, Heat Shock Protein 60; *BMI*, body mass index; *miR-29c*, MicroRNA-29c; *TNF-α*, Tumor Necrosis Factor-α; *IL-1β*, Interleukin-1β; *HucMSCs*, Human Umbilical Cord Mesenchymal Stem Cells; *ECM*, extracellular matrix.

translational potential of exosome-based delivery systems in treating age-related muscle atrophy.

Studies on other miRNA family members provide context and reference for understanding the regulatory network of miR-29c. For example, miR-34b has been shown to promote muscle growth and development *in vivo* by targeting SYISL and regulating its downstream genes p21 and MyoG (Wu et al., 2025). In addition, angiotensin II-induced muscle atrophy via PPARγ suppression is mediated by miR-29b; PPARγ acts as a negative regulator of miR-29b, and inhibition of miR-29b prevents such atrophy. IGF1, PI3K (p85α), and YY1 have been identified as target genes of miR-29b (Li et al., 2021). These findings reveal the important role of miR-29/34 family members in muscle homeostasis. Collectively, studies in aging or stress models outline a key network of miRNAs in the regulation of muscle mass, providing an evolutionary and mechanistic context for understanding the function of miR-29c in sarcopenia. Although the mechanistic insights from these related miRNAs are instructive, miR-29c in exercise-derived exosomes likely plays a central role in maintaining muscle protein homeostasis through its own unique, exercise-stress-adapted regulatory network. This suggests that promoting the release of miR-29c-enriched exosomes via exercise, or developing them as biologics, could become an innovative strategy to improve muscle protein metabolic imbalance in patients with sarcopenia. Future studies should focus on whether exercise-induced exosomal miR-29c signaling is sufficient to counteract sarcopenia progression in aged individuals and how this pathway can be optimized for better clinical outcomes.

3.3 Regulating the inflammatory microenvironment

Extracellular vesicles play a crucial role in regulating the microenvironment of muscle inflammation, and this process is essential for improving chronic low-grade inflammation and reversing muscle regeneration disorders in sarcopenia. The dysregulation of the inflammatory microenvironment is one of the key factors hindering effective muscle regeneration in the process of aging and sarcopenia. After muscle injury, exosomes can modulate the polarization state of macrophages, promoting their shift from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. Exosomes enriched with miR-125b-5p effectively induce M2 macrophage polarization, thereby supporting the activation of muscle stem cells and muscle repair (Li D. et al., 2025; Chazaud, 2020; Yang et al., 2025). The immune regulatory mechanism mediated by this extracellular vesicle is of great significance for correcting the chronic inflammatory state that persists in aging muscles and is not conducive to regeneration.

In the context of chronic inflammation in sarcopenia, this exosome mediated immune regulation is expected to break the pro-inflammatory cycle. The exosomes derived from human

umbilical cord mesenchymal stem cells (HucMSCs) pretreated with interleukin-1β (IL-1β) exhibit enhanced anti-inflammatory properties. Exosomes secreted by fibroadipogenic progenitors (FAPs) can promote the activation of muscle stem cells and muscle regeneration by carrying specific microRNAs (Yu et al., 2024), among which miR-206 regulates the deposition of muscle extracellular matrix and the remodeling of muscle tissue (Spinazzola and Gussoni, 2017), improve the inflammatory microenvironment that is unfavorable for regeneration, thereby promoting muscle cell regeneration (Chen et al., 2025).

This suggests that targeting the inflammatory microenvironment may be an important strategy for intervening in sarcopenia. In addition to regulating the proliferation and differentiation of muscle stem cells, exosomes can directly promote the formation and regeneration of muscle fibers by carrying growth factors and other signaling molecules (Luo et al., 2024; Porcu et al., 2024). Exosomes derived from human skeletal muscle cells can induce adipocyte-derived stem cells to undergo myogenesis and significantly improve muscle regeneration in muscle injury models (Luo et al., 2024). These findings collectively indicate that extracellular vesicles play an indispensable role in regulating the inflammatory microenvironment of muscles and promoting regeneration through multiple mechanisms, providing new ideas for intervening in sarcopenia characterized by inflammation and regeneration defects. Future research can further explore the potential of extracellular vesicles in the treatment of muscle diseases, especially for sarcopenia, an aging related disease, and develop extracellular therapeutic strategies based on extracellular vesicles (Wan et al., 2022; Cobelli et al., 2017).

4 Exosomes: an innovative direction for sarcopenia treatment

In the context of aging and sarcopenia, identifying effective strategies to intervene in regenerative impairment is crucial. The maintenance and decline of skeletal muscle regenerative capacity represent central issues in elucidating the pathogenesis of sarcopenia and developing intervention strategies. Owing to their unique biological properties, exosomes are emerging as a highly promising research direction in this field. The self-regeneration of skeletal muscle primarily relies on the fusion of satellite cells with damaged muscle fibers to achieve repair and remodeling (Bi et al., 2018). However, during the progression of aging and sarcopenia, satellite cell numbers decrease significantly, their function declines markedly, and the distance between satellite cells and capillaries increases, leading to dysregulated transmission of activation signals and further impairing muscle remodeling and regenerative capacity (Joanisse et al., 2017). Notably, sarcopenia exerts a more pronounced impact on fast-twitch muscle fibers in the elderly. Compared to corresponding slow-twitch fibers, these fibers exhibit lower expression levels of myosin, actin chaperones, and proteasome activity, which exacerbates functional loss and complicates repair in aged muscle (Murgia et al., 2017; Purves-Smith et al., 2014; Larsson et al., 2019).

In this context, the role of exosomes in the regulation of aged muscle regeneration is becoming increasingly prominent: exosomes can carry non-coding RNA molecules such as miRNAs, participating in the fine regulation of skeletal muscle regeneration. miRNAs are involved in post-transcriptional gene regulation through mRNA degradation or translational inhibition. In aged muscle, the dysregulated expression of multiple key miRNAs is associated with regenerative deficits. Skeletal muscle is rich in functionally specific miRNAs, such as miR-1, miR-133, miR-206, and miR-486 (Hausser and Zavolan, 2014; Zhang et al., 2014; Wang et al., 2012; Iwakawa and Tomari, 2015). The expression levels of miR-133b and miR-181a-5p are significantly upregulated in exercise-induced exosomes, which may contribute to muscle remodeling and homeostasis maintenance by modulating satellite cell activation and muscle regeneration-related pathways (Guescini et al., 2015); miR-31 can regulate the translation of the satellite cell activator Myf5, directly influencing the muscle regeneration process (Lovet et al., 2018; Crist et al., 2012); miR-23a/27a can also reduce myofiber loss by inhibiting muscle atrophy-related genes (Zhang et al., 2018).

Most of these miRNAs are secreted via extracellular vesicles such as exosomes and delivered to target cells, forming a trans-cellular regulatory network (Sun et al., 2018). Of particular note is that aging may alter the miRNA cargo profile of exosomes. Conversely, if muscle-derived exosomes carry aging-associated miRNAs (e.g., miR-34a-5p), they may induce senescence in skeletal stem cells and exacerbate regenerative impairment (Fulzele et al., 2019). This reveals a potential shift in exosome function from pro-regenerative to pro-senescent during aging, offering specific molecular targets for therapeutic intervention. Exosomes possess strong signal-transduction capabilities. Exosomes derived from human skeletal muscle cells can trigger the myogenic differentiation of stem cells, providing important biochemical cues for muscle regeneration. The myogenic growth factors they carry likely play a central role in this process (Choi et al., 2016). Meanwhile, a study by Mobley et al. was the first to demonstrate that whey-protein-derived exosomes can increase muscle protein synthesis and hypertrophy *in vitro*, possibly by up-regulating translation initiation factors. This mechanism operates independently of the mTOR signaling pathway, suggesting a distinct mode of anabolic regulation (Mobley et al., 2017). These findings provide a theoretical basis for using exogenous or engineered exosomes to bypass intracellular signaling defects in aged cells and directly stimulate anabolism.

Exosomes can be engineered into targeted delivery systems carrying specific DNA, RNA, proteins, or drugs. This property has demonstrated research value in various disease models, such as sarcopenia, type 2 diabetes, hind-limb ischemia, temporomandibular joint osteoarthritis, sepsis-induced kidney injury, myocardial infarction, Parkinson's disease, and gastric cancer (Nam et al., 2020; Le Bras, 2018; Tran et al., 2020). Applying this property to aging-related sarcopenia research would enable precise modulation of core pathological processes-including satellite-cell dysfunction, inflammatory microenvironment disturbance, and protein-metabolic imbalance-offering broad prospects for developing individualized intervention strategies. By regulating satellite-cell function, balancing miRNA regulatory networks, mediating intercellular signal transmission, and achieving targeted delivery, exosomes directly participate in key steps of skeletal muscle regeneration. They exhibit unique potential in reversing or delaying aging-related regenerative decline, undoubtedly providing a new perspective and a potential breakthrough for research on

skeletal muscle regeneration mechanisms and the development of sarcopenia prevention and treatment strategies.

A central and pressing translational question concerns the interplay between exercise intensity, age, and the release and function of exosomes. The release of exosomes exhibits a marked intensity-dependence. High-intensity exercise can more rapidly and substantially increase the number of circulating exosomes (Deng et al., 2021; Wa et al., 2025). However, older adults with sarcopenia are often unable to safely tolerate high-intensity training due to comorbidities, musculoskeletal risk, or functional limitations (Liu et al., 2022). Therefore, moderate-to low-intensity exercise becomes a more feasible alternative. Unlike the exosome profile enriched in "potent pro-regenerative" signals observed after high-intensity exercise in younger individuals, exosomes induced by moderate-to low-intensity exercise in older adults may carry a cargo biased toward molecules characterized as "protective," "adaptive," and "microenvironment-optimizing." These may include factors that improve vascular function and perfusion, molecules that effectively suppress chronic inflammation, effectors that enhance autophagy and cellular clearance, and signals that promote metabolic flexibility (Lai et al., 2023; Wang et al., 2020).

Such exosomes may partly compensate for the reduced "potent pro-regenerative" signals resulting from limited exercise intensity by optimizing the inflammatory and fibrotic microenvironment of aged muscle, enhancing the sensitivity of residual satellite cells to limited mitogenic signals, and improving overall tissue metabolic health-thereby supporting the maintenance and repair of aged muscle (Li et al., 2019; Sun et al., 2025; Liu et al., 2024). Future studies urgently need to directly compare the molecular profiles of exosomes released by individuals of different ages under different exercise intensities. This will clarify how aging alters the exercise–exosome response and identify the most effective "exercise–exosome" signatures for improving sarcopenia in the older population, laying the groundwork for developing precise exercise prescriptions or exosome-based alternative therapies.

5 Conclusion

The pathological core of sarcopenia lies in the synergistic interplay of imbalanced protein synthesis and degradation, autophagy-mitochondrial axis dysfunction, chronic low-grade inflammation, and the functional decline of muscle stem cells coupled with microenvironmental dysregulation, which collectively drive the progressive loss of skeletal muscle mass and function. As a safe and accessible non-pharmacological intervention, exercise integrates multiple physiological stimuli-including mechanical stress, calcium signaling, metabolic stress, and neuroendocrine regulation—to markedly enhance the release of circulating exosomes derived from diverse tissue sources. These exercise-induced exosomes carry a rich cargo of proteins, lipids, and nucleic acids, forming a systemic intercellular communication network. This review systematically elucidates the multi-layered reparative mechanisms by which exercise-derived exosomes counteract sarcopenia: alleviating muscle lipotoxicity through pathways such as activation of the FGF21-adiponectin axis; dually regulating protein metabolism via key molecules like miR-29c, which suppresses ubiquitin–proteasome-mediated catabolism while promoting satellite cell-driven anabolism; and improving the chronic inflammatory microenvironment by modulating macrophage polarization, thereby creating a favorable milieu for muscle regeneration. Together, these mechanisms directly target the core pathological processes of sarcopenia, reflecting the role of exosomes as a molecular bridge conveying the systemic benefits of exercise to local tissue repair.

Exercise-derived exosomes represent a highly promising novel target for the prevention and management of sarcopenia. Future research should aim to: clarify the specific regulatory effects of different exercise modalities on exosomal secretion profiles and molecular cargo; validate the therapeutic efficacy of specific exosome subpopulations in aging and sarcopenia animal models, while exploring engineering strategies to enhance their targeting and functional specificity; and conduct clinical studies to characterize exosome responses to exercise in older adults with varying health statuses, thereby laying a translational foundation for developing personalized exercise prescriptions or exosome-based biologics.

Author contributions

XW: Conceptualization, Writing – original draft. HH: Conceptualization, Writing – review and editing. JC: Writing – review and editing, Supervision. QZ: Formal Analysis, Writing – original draft. ZY: Investigation, Writing – original draft. MY: Writing – review and editing. CP: Supervision, Writing – review and editing. SL: Supervision, Writing – review and editing.

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