# Exercise-induced extracellular vesicle microRNA regulates physiological function (Review)

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**Abstract.** Physical exercise is essential for maintaining health and preventing disease. Various forms of exercise enhance physiological function by regulating multiple body systems, including the metabolic, immune, cardiovascular and nervous systems. Beyond directly improving organ performance, exercise promotes systemic homeostasis through the modulation of extracellular vesicles (EVs), particularly exosomes. Functioning as key mediators of intercellular communication, exosome-derived microRNAs (miRNAs) exhibit dynamic regulation influenced by exercise type, frequency and intensity. Accumulating evidence suggests that exercise-induced exosomal miRNAs support organ integrity and play crucial roles in the prevention and treatment of disorders associated with the metabolic, immune, cardiovascular and nervous systems. Elucidating the underlying cellular and molecular mechanisms of these miRNAs may enable their application as diagnostic biomarkers and therapeutic targets for a variety of diseases. The present review summarized advances in the study of exercise-induced exosomal miRNAs and underscored their potential in promoting health and preventing disease.

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## 1. Introduction

Physical exercise is considered to play an essential role in maintaining a healthy lifestyle and exercise is essential for maintaining health and preventing disease (1). Exercise regulates metabolism, supports immune function and enhances cardiovascular and nervous system activity, making it a multifaceted intervention with broad public health benefits (2). Traditionally, the bodily adaptations induced by exercise have been understood in terms of improved organ function, increased endurance and enhanced strength (3). Recent study, however, has shown a more complex understanding of the relationship between exercise and health, especially the notable role of extracellular vesicles (EVs), including exosomes, played in this relationship (4,5). The interaction between exercise and exosomes is a complex and intriguing research direction. Delving into this relationship holds notable academic and clinical importance for revealing the impact of exercise on physiological functions.

Exosomes, a specific subtype of EVs, are small, single-membrane, secreted organelles of 30-200 nm in diameter that have the same topology as the cell and are enriched in selected proteins, lipids, nucleic acids and glycoconjugates (6). These nanoscale vesicles transmit diverse signaling molecules between cells and tissues, such as microRNA (miRNA), messenger RNA and mitochondrial DNA, modulating physiological responses through autocrine and paracrine methods (7,8).

Exosomes offer several notable advantages over other delivery mediums: They can transmit diverse signals simultaneously, facilitate the delivery of multiple miRNAs, exhibit marked targeting specificity, shield signaling molecules from enzymatic degradation, enhance synergistic signal transduction and participate in the post-transcriptional regulation of gene expression (9-11). EVs also play marked roles in fundamental cellular processes, including survival, differentiation, proliferation and metabolism (12-14). Nearly all cell types secrete exosomes, which are nanoparticles capable of

interacting with proximate cells or entering distant organs and tissues (11,15). Upon entering a recipient cell, exosomes release bioactive substances that modulate protein expression and activate various signaling pathways (16).

Exosomes also carry an array of surface molecules, including adhesion molecules, integrins, and tetraspanins (CD9, CD63, CD81 and CD151), which facilitate interactions with target cells by binding to transmembrane receptors and ligands (17-19). Exosomes can also enter recipient cells through endocytosis or directly traverse the cell membrane, incorporating proteins into their exosomal membranes (20). The multifunctionality and widespread distribution of exosomes underscore their marked potential and utility in the fields of medicine and biology.

Exercise-induced exosomal signaling molecules influence both adjacent and distant cells during the adaptive processes initiated by physical activity, directly contributing to the regulation of intercellular signaling pathways (20). The release of exosomes during exercise involves intricate cellular signaling pathways, representing dynamic adjustments within the cellular microenvironment. Understanding how different forms of exercise regulate exosome release, as well as how these exosomal signaling molecules modulate cellular functions, is needed to unravel the broader physiological impacts of exercise (21-23).

The present review aimed to comprehensively examine the relationship between exercise-induced alterations in exosomal miRNAs and their implications for disease pathophysiology. By elucidating these connections, it aimed to advance the understanding of the intricate interplay between exercise and health, thereby identifying potential therapeutic targets for the prevention and management of exercise-related diseases.

## 2. Impact of exercise on the production and release of exosomes

Advances in cellular biology have established skeletal muscle as a dynamic endocrine organ capable of systemic communication through EVs, particularly exosomes (24,25). These vesicles play a notable role in regulating physiological responses to physical activity by delivering molecular signals to distant tissues.

Research has shown that skeletal muscle releases exosomes into the circulation, with evidence of their presence in distant and contralateral muscles, supporting their paracrine-like effects (26). The biogenesis of exosomes begins with endocytosis, where the cell membrane invaginates to form early endosomes (27). These early endosomes undergo maturation into late endosomes, which involves marked biochemical remodeling, including the reorganization of membrane proteins and lipids; this process ultimately leads to the formation of multivesicular bodies (MVBs) (28). Through complex regulatory mechanisms, such as the activity of endosomal sorting complexes required for transport proteins, MVBs fuse with the cell membrane to release exosomes into the extracellular environment (28).

Exosomes circulate via the bloodstream or lymphatic system, delivering proteins, RNA and signaling molecules to recipient cells, thereby regulating their functions (27). Exercise markedly influences the production and composition of exosomes. In healthy individuals, exercise can acutely increase circulating exosome levels by ~1.5-3-fold, particularly through physiological stressors such as mechanical strain and oxidative stress, which activate signaling pathways during muscle contraction (29). For example, increased intracellular $Ca^{2+}$ levels trigger key pathways such as mTOR and AM-activated protein kinase, which regulate cellular metabolism and stress responses, directly impacting the quantity and molecular composition of exosomes (30,31). The illustrated process of exosome formation, highlighting the molecules and information transfer pathways involved is illustrated in Fig. 1. This depiction provides a representation of the formation and fusion of intracellular vesicles, the loading mechanisms of miRNAs and other molecules, and the pathways of exosome-mediated intercellular communication.

Exercise modulates the dynamics of exosomes in a pattern dependent on intensity, type and duration, leading to variations in both their abundance and molecular composition within circulation. High-intensity exercise, characterized by pronounced oxidative stress, tends to provoke robust changes in exosome secretion and cargo loading, particularly enhancing the release of vesicles carrying stress-related or inflammatory molecules such as specific miRNAs (e.g., miR-133a, miR-133b and miR-206) and proteins (e.g., HSP70 and IL-6) (32,33). By contrast, moderate- or low-intensity exercise (typically 45-65% $VO_2$ max) induces only mild or inconsistent increases in exosome number but still reshapes miRNA signatures and other molecular cargos, particularly those related to oxidative stress regulation, endothelial protection and inflammatory modulation (34,35).

Different exercise modalities lead to distinct EV profiles, with variations in abundance, surface markers and molecular cargo depending on exercise type and intensity. For example, endurance training markedly increases exosomal miRNAs such as miR-136-3p and miR-342-5p, both of which are involved in tissue adaptation and cardioprotection. Interval training, including high-intensity bouts, produces robust changes in specific exosomal markers and a rapid increase in proteins linked to oxidative stress response and cell signaling (29,36-38).

Trained individuals typically demonstrate more efficient vesicle clearance, meaning that their exosomal profiles return to baseline faster after exercise, and they exhibit distinct miRNA responses compared with untrained subjects. For instance, well-trained older men show altered miRNA expression in exosome-enriched EVs after exercise, indicating durable changes in tissue communication and adaptation pathways. Sedentary individuals, by contrast, may have less pronounced or less efficient exosomal responses (26,39).

These findings collectively highlight that both the qualitative and quantitative features of exercise-induced exosome release, such as miRNA and protein signatures, are determined by the specific modality and intensity of exercise, as well as the training status of the individual.

In conclusion, exercise serves as a potent biological modulator, shaping the production, molecular cargo, and functions of exosomes in an activity-dependent manner. Investigating these mechanisms not only provides valuable insights into the physiological benefits of exercise but also offers promising therapeutic avenues for the treatment of metabolic and inflammatory diseases.

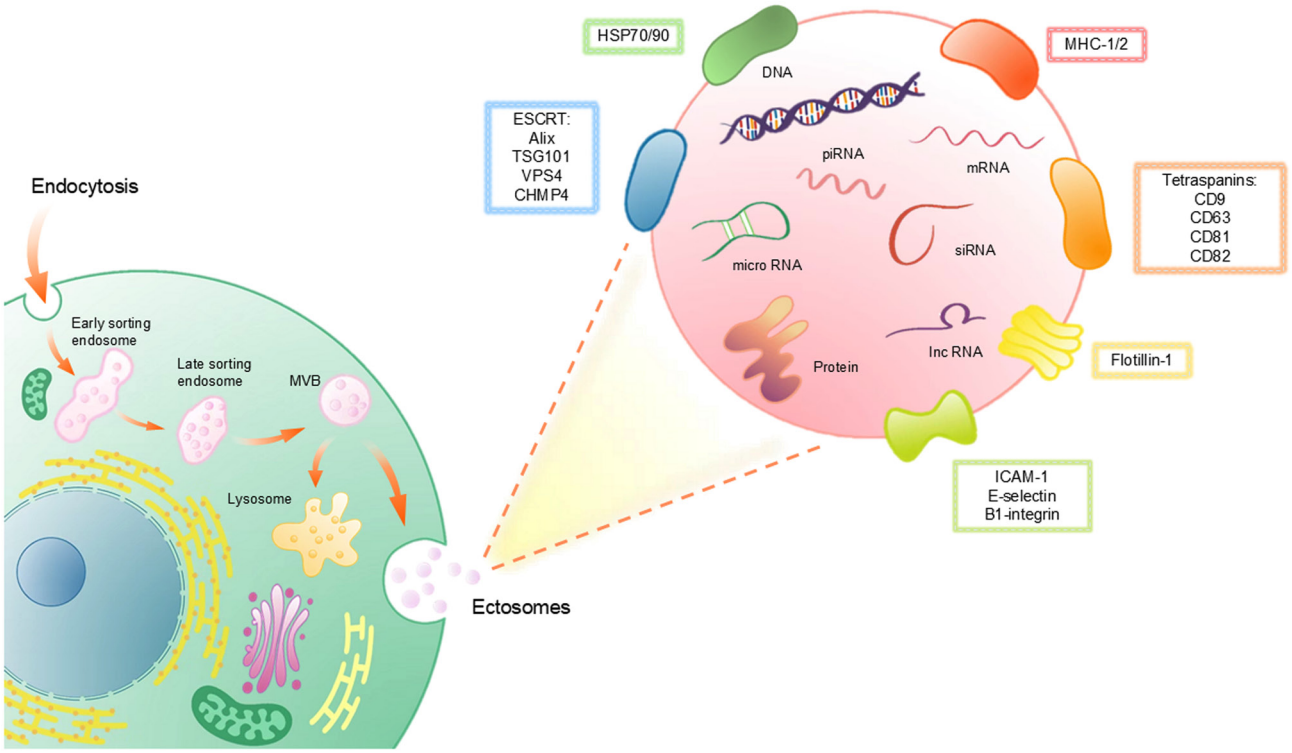


Figure 1. Biogenesis, composition and molecular cargo of EVs. EVs are generated through the endocytic pathway, beginning with early sorting endosomes that mature into late sorting endosomes and subsequently form MVBs. Upon fusion of MVBs with the plasma membrane, intraluminal vesicles are released as exosomes, whereas fusion with lysosomes leads to cargo degradation. The schematic highlights the diverse molecular cargo carried by EVs, including nucleic acids (DNA, mRNA, miRNA, siRNA, piRNA and lncRNA), proteins and membrane-associated molecules. EV membranes are enriched with tetraspanins (CD9, CD63, CD81 and CD82), HSPs (HSP70/90), flotillin-1, MHC-I/II and adhesion molecules such as ICAM-1, E-selectin and β1-integrin. The ESCRT, including Alix, TSG101, VPS4 and CHMP4, are involved in EV biogenesis and cargo sorting. EVs, extracellular vesicles; MVBs, multivesicular bodies; miRNA, microRNA; siRNA, small interfering RNA; piRNA, Piwi-interacting RNA; lncRNA; HSP, heat shock protein; MHC-I/II, major histocompatibility complex class I and II; ICAM-1, intercellular adhesion molecule-1; ESCRT, endosomal sorting complexes required for transport; Alix, ALG-2-interacting protein X; TSG101, tumor susceptibility gene 101 protein; VSP4, vacuolar protein sorting-associated protein 4; CHMP4, charged multivesicular body protein 4.

## 3. Impact of exercise-induced exosomal miRNAs on different organs

Exercise-induced exosomal miRNAs regulate and protect various body systems by influencing the muscular, metabolic, cardiovascular, nervous and immune systems (Fig. 2).

*Multilevel metabolic regulation involving exercise-induced exosomal miRNA release*. Exercise is not only a source of physical vitality but also a key driver of micro-metabolic regulation. In this process, exosomes play a pivotal role in serving as nano-messengers of intercellular communication, carrying regulatory information related to energy metabolism, lipid metabolism, glucose metabolism, immune regulation and metabolic communication between organs, thereby constructing a detailed and complex metabolic balance network (40). Muscle-derived exosomes produced during exercise may contain molecules that enhance insulin sensitivity or promote fat oxidation (33). These finely tuned molecular mechanisms make exosomes play a marked role in regulating the body's response to exercise, particularly in energy metabolism and cellular signal transduction.

Studies have shown that muscle-derived exosomes play a notable role in enhancing insulin sensitivity and promoting fat oxidation; for instance, one study demonstrated that exosomes from skeletal muscles can enhance insulin sensitivity in mice by downregulating hepatic FoxO1 (33). Additionally, it was found that exosomes from muscles of mice on a high-fat diet had enlarged isolated islets *in vitro* and induced proliferation of insulin-secreting cells, suggesting a potential role of exosomes in influencing insulin secretion (41). In addition, exosomes are hypothesized to regulate insulin sensitivity by modulating inflammation or through direct interactions with insulin-responsive organs, such as the phosphatidylinositol 3-kinase/Akt signaling pathway (42). These findings demonstrate the potential of muscle-derived exosomes in impacting insulin sensitivity and fat oxidation, revealing their involvement in exercise-regulated energy metabolism and cellular signal transduction. Another study found that in patients with type 2 diabetes, the concentrations of EVs produced by endothelial cells, platelets and monocytes were notably elevated (43), suggesting that the higher concentrations of EVs in diabetics compared with healthy subjects might be related to insulin resistance exacerbating vesicle release (44). Exercise can directly enhance insulin sensitivity by increasing skeletal muscle glucose uptake, thereby helping to lower blood glucose levels in patients with type 2 diabetes (45). Exercise can reduce serum exosomal miR-27a levels, which is considered a key regulator of PPAR-γ, thereby affecting adipose tissue browning and insulin sensitivity (46). In addition, exercise training can effectively improve adipocyte dysfunction caused by intermittent hypoxia (reducing insulin resistance) by adjusting

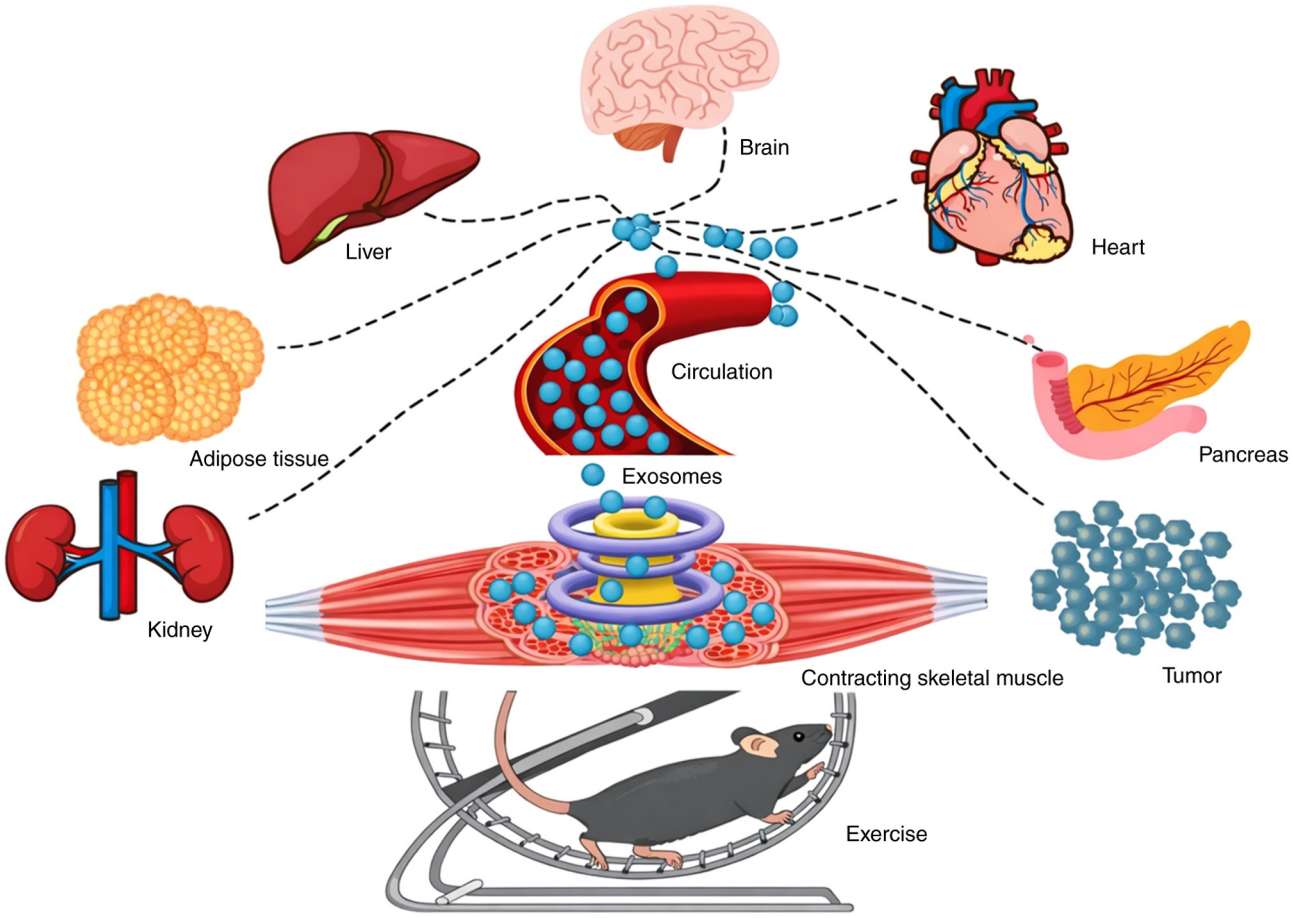


Figure 2. Interorgan communication mediated by exercise-induced exosomes. During exercise, contracting skeletal muscle releases exosomes into the circulation, which act as key mediators of interorgan communication. These circulating exosomes can be transported via the bloodstream to multiple peripheral organs, including the brain, heart, liver, adipose tissue, kidney and pancreas, as well as to pathological tissues such as tumors. Exercise-induced exosomes carry diverse bioactive cargoes, including microRNAs, proteins and other signaling molecules, which modulate metabolic regulation, cardiovascular function, neural activity, immune responses and tissue remodeling in target organs. Conversely, non-muscle organs can also release exosomes into the circulation that act on skeletal muscle, thereby influencing muscle metabolism, mitochondrial function, and adaptive responses under physiological and pathological conditions.

gut microbiota balance, reducing intestinal permeability and optimizing plasma exosomal cargo (47). Furthermore, exercise has also been shown to reduce elevated plasma EV concentrations in obese individuals (48). A study by Kawanishi *et al* (49) showed that long-term exercise can regulate EV expression, inhibit macrophage infiltration in adipocytes and reduce Toll-like receptor 4 expression, aiding in the transition of macrophages from the M1 pro-inflammatory phenotype to the M2 anti-inflammatory phenotype, thereby alleviating inflammation and enhancing insulin sensitivity. Glucose tolerance can also be improved by exercise training, and plasma triglyceride levels can be reduced by altering the miRNA spectrum in circulating exosomes (such as marked increases in miR-133a and miR-133b). Exercise-induced exosomal miRNA changes, such as marked increases in miR-133a and miR-133b, can also reduce FoxO1 expression in the liver, thereby impacting systemic metabolic characteristics. These numerous studies prove the notable role of muscle-released exosomes in improving the metabolic system through exercise (33).

Further research in this direction may guide clinical researchers in developing targeted interventions to improve insulin sensitivity and metabolic health. By regulating metabolism through exercise-induced exosomes, insight is gained into a multilevel, synergistic network of energy and metabolic balance. This provides a valuable perspective for understanding the comprehensive impact of exercise on body metabolism and offers strategic targets for future research and treatment of metabolic-related diseases.

*Impact of exercise-induced exosomal miRNAs release on the cardiovascular system*. Exercise, as a crucial factor in maintaining cardiovascular health, especially in the modulation of exosomes and their miRNA expression profiles. Exercise plays a crucial role in maintaining cardiovascular health in part by modulating exosome release and their miRNA expression profiles. Accumulating evidence indicates that exercise-induced exosomes exert cardioprotective effects through anti-inflammatory actions, regulation of lipid metabolism and oxidative stress, and modulation of immune cell function, thereby contributing to the attenuation of atherosclerosis and the protection, survival and repair of cardiomyocytes (50). For example, Ruan *et al* (51) found that Suxiao Jiuxin Pill, a commonly used medication for angina pectoris and coronary heart disease, could promote the secretion of exosomes derived from mouse myocardial mesenchymal stem cells, thereby protecting against myocardial

ischemia/reperfusion injury; however, the specific molecular cargo and underlying mechanisms of these exosomes were not further characterized. Long-term exercise training plays a key role in cardiac protection through circulating exosomes, effectively preventing damage caused by myocardial ischemia and reperfusion. Notably, miRNAs in these exosomes, especially miR-342-5p, are markedly increased in both human and animal models undergoing exercise training. miR-342-5p targets cysteine-aspartic protease-9 (caspase-9) and Jnk2 to reduce myocardial apoptosis induced by hypoxia/reoxygenation, while promoting Akt phosphorylation via regulation of the phosphatase gene *Ppm1f*. In animal models and endothelial cell systems, exercise training and laminar shear stress have been shown to upregulate miR-342-5p expression, supporting its role in exercise-associated cardioprotective mechanisms (37). Exercise-induced exosomes also positively impact cardiovascular microcirculation by improving tissue blood supply and oxygenation through growth factors and miRNAs, such as the upregulation of miR-126 levels in endothelial progenitor cell-derived exosomes in response to moderate-intensity aerobic treadmill exercise, alleviating apoptosis in endothelial cells (ECs) induced by high glucose and promoting EC migration and tube formation (52). Exercise, by modulating exosome components, improves the angiogenic potential in patients with type 2 diabetes, increasing the expression of SOD3 and ATP7A proteins in plasma exosomes, thus promoting angiogenic responses. Experiments have shown that exercise training restores the impact of exosomes from type 2 diabetic mice on endothelial cell angiogenesis, revealing the key role of SOD3 in exercise-induced angiogenesis. Therefore, exosomal SOD3 can serve as a type of exercise-mimetic therapy, supporting angiogenesis and wound repair in cardiovascular diseases (53).

In summary, exercise-induced exosomes play a notable role in regulating endothelial cell functions, anti-inflammatory actions, slowing down atherosclerosis, protecting myocardial cells and improving cardiovascular microcirculation.

*Impact of exercise-induced exosomal miRNAs release on the immune system*. miRNA are notable regulatory factors in the immune system, being small non-coding RNA molecules responsible for inhibiting the expression of specific genes, thereby affecting the behavior of immune cells (54). These small molecules play a marked role in the differentiation, proliferation, activation and cytokine production of immune cells such as T cells, B cells, macrophages and dendritic cells (55-58). Research on immune-related miRNAs is summarized in Table I, which details the miRNAs closely related to immune functions (59-80).

Studies have shown that exercise can affect the release of exosomes and their miRNA components, which can be absorbed by immune cells and influence intracellular gene expression, thus modulating the immune response (81). Specifically, exercise-associated EV-miRNAs, such as miR-21, miR-146a and miR-126, have been reported to regulate inflammatory signaling by promoting anti-inflammatory cytokines including interleukin-10 (IL-10) while suppressing pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-6, thereby contributing to immune homeostasis (81). After intense exercise or long-term training, this regulation helps to reduce chronic inflammation and excessive immune responses, enhancing the defense of the immune system against pathogens (22).

Beyond enhancing muscle function and endurance, exercise also modulates immune and inflammatory responses, as exercise-induced tissue damage and metabolic changes can trigger inflammation, which is subsequently regulated by exercise-induced exosomes transferring specific miRNAs such as miR-146a to promote tissue repair and recovery (81). This alteration in miRNA helps control post-exercise inflammatory responses, reducing tissue damage and accelerating recovery. By regulating inflammatory responses, these miRNAs help maintain the balance of the immune system, prevent overreactions, and protect the body from the effects of chronic inflammation, which is especially important for athletes engaged in high-intensity exercise over the long term.

The changes in miRNAs within exercise-induced exosomes are not only notable for regulating normal immune responses and controlling inflammatory responses but may also play a role in preventing and treating various diseases. For example, specific miRNAs may reduce the risk or severity of autoimmune diseases by modulating immune cell functions (22,82). These miRNAs have potential therapeutic value in regulating autoimmune responses and preventing excessive immune activities. Since these miRNAs can be transported long distances within the body via exosomes, they have the potential to be non-invasive biomarkers for monitoring immune status, inflammatory responses and response to exercise interventions (83).

Overall, exercise-induced exosomes have a marked and extensive effect on the immune system. These exosomes play a role in regulating the activity of immune cells, balancing inflammatory responses, enhancing immune surveillance and memory formation (81). Although research has provided important insights, further exploration is needed to understand precisely how exercise regulates the specific mechanisms of exosomes. Future research should focus on the specific mechanisms of action of exercise-induced exosomes in different types of immune cells and how these exosomes exhibit variations in different exercise modalities and among different populations. Additionally, exploring the potential clinical applications of exercise-induced exosomes, especially in the prevention and treatment of immune diseases, will be a valuable research direction.

*Impact of exercise-induced exosomal miRNAs release on the nervous system*. The interaction between exosomes and neural cells plays a key role in the nervous system. Neurons and glial cells communicate and regulate the functions of each other by releasing exosomes. First, exosomes facilitate direct information exchange between neurons and glial cells; neurons release exosomes carrying specific miRNAs, proteins and other signaling molecules, which can be taken up by surrounding glial cells, affecting their functions and states (84). Similarly, glial cells also release exosomes, exerting regulatory effects on surrounding neurons (85). Exercise-stimulated exosomes markedly impact neural cell repair and regeneration; long-term exercise improves the blood-brain barrier function in Alzheimer's disease mouse models and facilitates the clearance of amyloid-β (86). Exosomes isolated from the brains

Table I. MiRNAs closely related to immune function.

| miRNA | Functions | (Refs.) |
|---|---|---|
| miR-155 | Modulates inflammatory responses, regulating the activation and response of various immune cells. | (59) |
| miR-146a/b | Promotes the resolution of inflammation by producing pro-inflammatory cytokines within inflammatory pathways, exerting regulatory functions. | (60-62) |
| miR-21 | Regulates T cell functions, proliferation and immune suppression, and is involved in promoting cell proliferation, invasion and the survival of activated T cells. | (63-66) |
| miR-181a/b | Regulates T cell development and function, playing a role in immune tolerance. | (67,68) |
| miR-223 | Acts as a potent regulator of granulocyte, macrophage and dendritic cell differentiation and proliferation during inflammation. | (69) |
| miR-124 | Influences the immune response of the nervous system, regulating microglia and immune modulation within brain tissue. | (70,71) |
| miR-17-92 | Regulates the proliferation and survival of T and B lymphocytes, affecting the balance of immune responses. | (72,73) |
| miR-125b | Has a notable regulatory role in the proliferation and differentiation of immune cells, potentially playing a role in autoimmune diseases. | (74) |
| miR-150 | Regulates the development and function of T and B lymphocytes, particularly playing a notable role in the differentiation of lymphocyte subsets. | (75) |
| miR-132 | May affect inflammation and immune responses, involved in modulating the functions of T cells and dendritic cells. | (76,77) |
| miR-29 | Controls the activation state of T cells and macrophages, participating in the regulation of inflammatory responses and immune tolerance. | (78,79) |
| miR-30 | Affects the maturation, proliferation, differentiation, and activation of various immune cells, associated with autoimmune diseases and also involved in the regulation of antibody production. | (80) |

miRNA, microRNA.

of exercising mice can improve pericyte and endothelial cell functions, upregulating platelet-derived growth factor receptor β, zonula occludens-1 and claudin-5 expression. Exercise also regulates the expression of miR-532-5p in exosomes, thus affecting brain cell functions (87). Another study investigating EV characteristics and EV-related miRNAs post-rest and aerobic exercise in cerebral palsy and typically developing individuals found reduced EV concentration and increased circulating miR-486 in patients with cerebral palsy. These findings suggest an association between exercise-related alterations in circulating EV-miRNA profiles and skeletal muscle-related transcriptional regulation. Functional analyses indicated that miR-486 may influence myogenic gene expression; however, its direct role in cerebral palsy pathology and effects on neural cell types were not directly examined (88). In summary, exosomes may regulate nervous system functions and information transmission by directly interacting with neurons and glial cells and potentially interacting with the blood-brain barrier. Although the mechanisms by which exosomes cross the blood-brain barrier still need further research, hypotheses regarding these mechanisms have been proposed, including transcytosis, paracellular and transcellular pathways (89) jumping from one cell to another through MVB compartments (90) and passive diffusion (91).

The effect of signal molecules carried by exercise-induced exosomes on neural cells is a subject of interest. Exercise-induced exosomes have been shown to promote synaptic growth, regulate neural plasticity and enhance neural maturity (92). Further research indicates that exosomes from exercise can alleviate anxiety, improve neurogenesis, regulate neuroinflammation and promote neurological localization, demonstrating their potential in treating certain neurological diseases (93,94). Exosomes are involved in complex biological processes of neural regeneration, neuroprotection and neural plasticity; accumulating evidence indicates that miRNAs carried by exosomes can regulate neural stem cell differentiation and promote neural regeneration, providing a mechanistic basis for the neuroregulatory effects of exercise-induced exosomes. For example, a study found that exosomes from neural stem cells (NSCs) drove the differentiation of NSCs and promoted the maturation of neurons and glial cells, with miR-9 being most abundantly expressed in NSC-derived exosomes (95). Additionally, another study demonstrated that exosomal miR-21a derived from neural progenitor cells regulates neurogenesis by promoting neuronal differentiation in *in vitro* neural progenitor cell models (96). Research has also focused on the role of stem cell-derived exosomes and miRNAs in spinal cord injuries; results showed that specific miRNAs carried by bone marrow stem cell-derived exosomes, such as miR-126, miR-124-3p and miR-181c, can inhibit neuronal cell death and promote neuronal differentiation in spinal

cord injury models (97). Overall, these findings demonstrate the potential of miRNAs carried by exosomes in promoting the proliferation and differentiation of neural stem cells, which is notable for the development of new methods for studying neural regeneration and stimulating endogenous neurogenesis. In terms of neurotransmitter release, neural signal transduction and neuroinflammation, exosomes influence the synthesis and release of neurotransmitters in neurons by modulating miRNA transport methods (84). Exercise also affects exosome components, regulating neural transmission and neural plasticity. In the field of neuroscience research, early exercise intervention has shown notable effects in neuroprotection after a stroke. Through the release of exosomes, early exercise intervention after stroke inhibits excessive microglial activation and enhances synaptic plasticity, thereby improving neurological function, promoting body weight recovery and reducing cerebral infarct volume in rats, suggesting a potential exosome-mediated therapeutic mechanism applicable to other neurological disorders such as Alzheimer's disease and cerebral palsy (98). Additionally, exercise intervention helps reduce the number of microglia, enhance dendritic complexity and increase the expression of synaptophysin and postsynaptic density protein 95 (98). Exercise interventions increase the levels of exosomes in the serum of stroke rats, thereby promoting brain synaptic growth and the integrity of the corticospinal tract; this process aids in reducing infarction volume, improving neural function and rat gait. Exosomes play a key role during exercise, enhancing serum and brain exosome levels, beneficial for neural plasticity and neuroprotection (92). Exercise training, in conjunction with bone marrow MSC-derived exosomes (MSC-exos), and activation of the JNK1/c-Jun signaling pathway markedly reduce neuronal apoptosis and cerebral infarction volume, promoting synapse formation and axonal regeneration, thus effectively restoring neural function, showing improved effects compared with treadmill exercise or MSC-exos treatment alone (99). In the regulation of neuroinflammation, exercise-induced exosomes also play a notable role. Regarding neuroinflammatory responses, exosomes may modulate the inflammatory state of neural cells by carrying anti-inflammatory or pro-inflammatory molecules. A study demonstrated that the process of neuroinflammation can be promoted by miRNAs such as miR-155 or inhibited by miRNAs including miR-146a, miR-124 and miR-21. miR-124 influences a wide range of pathological processes, including mental illnesses and central nervous system injuries; and other miRNAs, such as the let-7 family, can promote or inhibit the induction of inflammatory responses (100). Exercise-released exosomes carrying anti-inflammatory molecules, such as miR-146a, miR-21 and miR-126, can attenuate neuroinflammation by suppressing pro-inflammatory signaling pathways (e.g., NF-κB) and modulating immune cell activation, thereby contributing to the prevention and treatment of neurodegenerative diseases (101). In summary, these exosomes, by carrying specific signaling molecules, participate in regulating physiological processes such as neurotransmitter release, neural signal transduction and neuroinflammatory responses. The molecules they carry may directly or indirectly affect the activity of neurons, neural signal transduction and inflammation. These findings underscore the notable role of exercise through exosomes in neuroprotection and stroke treatment strategies.

The role of exosomes in emotional regulation and stress response is also of note. They help alleviate stress and anxiety by regulating the release and balance of neurotransmitters, which is vital for maintaining mental health. A study showed that in patients with depression, there was an upregulation of has-miR-335-5p and a downregulation of has-miR-1292-3p in plasma exosomes, affecting signaling pathways related to synaptic density, axonogenesis and cell growth (102). These molecules may regulate the efficiency of information transmission between neurons, affecting neural signal transmission.

To study the role of exercise-induced exosomal miRNAs in these physiological processes, this information was collected in Table II to elucidate the effect of miRNAs on the nervous system (103-112). In summary, it has been demonstrated that exercise-induced exosomes play a notable role in the health and functionality of the nervous system. From promoting the repair and regeneration of neural cells, modulating neural transmission and plasticity, to controlling neuroinflammation and affecting mood regulation, exercise-induced exosomes offer new research perspectives and potential therapeutic options in the field of neuroscience.

Future studies need to further explore the specific mechanisms of action of exercise-induced exosomes in different types of neurological diseases. Particularly for age-related neurodegenerative diseases, such as Alzheimer's and Parkinson's, exercise-induced exosomes may play a key role in therapy and prevention. Additionally, research should investigate how different exercise modalities affect the characteristics and efficacy of exosomes and how these exosomes function in diverse populations, thus providing more personalized exercise prescriptions. Moreover, exploring the potential clinical applications of exercise-induced exosomes is also a notable direction for future research. For instance, using exosomes as biomarkers to assess the effects of exercise interventions or as potential carriers for treating neurological diseases. Overall, the role of exercise-induced exosomes in the nervous system underscores the importance of exercise as an effective neuroprotective strategy. As the understanding of this field improves, it can be expected that more discoveries about the interactions between exercise, exosomes and neural health will be made, providing new strategies for improving neural health and treating neurological diseases.

## 4. Exosome-mediated inter-organ communication targeting skeletal muscle

Exosomes derived from non-muscle organs have emerged as notable regulators of skeletal muscle physiology. While skeletal muscle functions as a secretory organ, it is also a recipient of exosomal signals originating from the brain, liver, adipose tissue and kidney (113). These organ-derived exosomes, enriched with tissue-specific miRNAs and other bioactive molecules, modulate muscle metabolism, mitochondrial function and adaptive responses under both physiological and pathological conditions (113).

Table II. Effects of exosomal miRNAs on the nervous system.

| miRNA | Functions | (Refs.) |
|---|---|---|
| miR-9 | Regulates neural development and synaptic plasticity. | (103) |
| miR-124 | Promotes neuronal differentiation and post-synaptic gene expression. | (104) |
| miR-132 | Participates in the development of neurons and synaptic plasticity. | (105) |
| miR-29 | Modulates the functions of neurons and glial cells. | (106) |
| miR-125 | Plays a role in synaptic formation and neuronal survival. | (107,108) |
| miR-134 | Regulates synaptic plasticity and post-synaptic gene expression. | (109) |
| miR-137 | Regulates neural development, synaptic formation and neurodegenerative diseases. | (110) |
| miR-206 | Affects neuronal growth and synaptic function. | (111) |
| miR-335 | Potentially regulates neural system development and neuronal apoptosis. | (112) |
| miR-431 | Influences neuronal development and synaptic plasticity. | (112) |
| miR-708 | Potentially involved in neuronal growth and synaptic development. | (112) |

miRNA, microRNA.

Brain-derived exosomes constitute a notable pathway for neuro-muscular communication. Neurons and glial cells release exosomes containing miR-124, miR-9 and miR-132, which can enter the bloodstream and reach peripheral skeletal muscles, where they contribute to the maintenance and regeneration of neuromuscular junctions (114). However, under conditions of neurodegeneration or inflammation, brain-derived exosomes may carry pro-inflammatory miRNAs, such as miR-155, miR-21 and miR-34a, which can exacerbate muscle atrophy and fatigue and ultimately impair neuromuscular signaling (114).

Similarly, the liver communicates with skeletal muscle via hepatocyte-derived exosomes carrying miRNAs such as miR-122, miR-192 and miR-21 (32). These vesicles influence muscle insulin sensitivity and lipid metabolism, and in metabolic disorders such as obesity and type 2 diabetes, increased levels of hepatic exosomal miR-122 have been shown to impair glucose uptake and mitochondrial function in skeletal muscle (115,116). Thus, exosomal miR-122 acts as a negative regulator in skeletal muscle, linking liver pathology to impaired muscle insulin sensitivity and mitochondrial health in metabolic diseases.

Adipose tissue also plays an integral role in this inter-organ communication network. Exosomes secreted by adipocytes are rich in miR-27a and miR-29a, which target the PGC-1α signaling pathway in skeletal muscle, suppressing mitochondrial biogenesis and promoting insulin resistance (117). Lifestyle modifications, particularly regular physical activity and caloric restriction, can reshape the miRNA profile of adipose-derived exosomes to promote metabolic health. Exercise and dietary interventions reduce the abundance of adipose-derived exosomal miRNAs such as miR-27a and miR-29a, which are associated with metabolic dysfunction, while concomitantly increasing exercise-responsive exosomal miRNAs involved in mitochondrial biogenesis, glucose metabolism and insulin signaling. Although the specific miRNAs upregulated vary across studies and intervention types, this overall remodeling of exosomal cargo facilitates healthier inter-organ communication and improves systemic metabolic balance (117-120).

The kidney also exerts regulatory effects on skeletal muscle physiology via exosomal signaling. Renal exosomes, detectable in both blood circulation and urine, carry uremic toxin-responsive miRNAs, including miR-223 and miR-26a. In chronic kidney disease, these vesicles may reach skeletal muscle and elicit inflammatory and oxidative stress responses, contributing to muscle wasting (41,121).

Collectively, these findings highlight a complex and dynamic exosome-mediated inter-organ communication network, wherein skeletal muscle acts not only as an exosome-secreting tissue but also as a responsive target of exosomal signals from distant organs. This bidirectional communication is modulated by metabolic status, pathological conditions and exercise interventions. A deeper understanding of how physical activity reshapes these exosome-mediated interactions will offer valuable insights into systemic adaptive mechanisms and may inform the development of novel therapeutic strategies for metabolic and neuromuscular diseases.

## 5. Future research directions and prospects

Exercise, as a critical lifestyle intervention, induces extensive physiological adaptations across multiple organ systems. Mounting evidence demonstrates that exercise regulates the biogenesis, molecular composition and functional dynamics of EVs, which exhibit considerable therapeutic potential in cardiovascular, neurodegenerative, metabolic, oncological and musculoskeletal disorders. Exercise-induced EVs exert multifaceted regulatory effects on recipient cells by modulating their secretion into circulation, remodeling their protein, lipid and nucleic acid cargo, and enhancing immune regulation and intercellular communication. Collectively, these processes facilitate tissue regeneration, attenuate inflammation and sustain systemic homeostasis. Consequently, exercise-derived EVs have emerged as a rapidly expanding field in biomedical research, offering new mechanistic insights and therapeutic avenues for health maintenance and disease management.

In cardiovascular diseases, EVs promote cardiac repair by stimulating angiogenesis and suppressing inflammation (35). In neurodegenerative disorders, they support neuronal survival and preserve cognitive function through the transfer of neurotrophic factors (84). In oncology, EVs enriched with tumor-suppressive molecules impede malignant progression and trigger apoptotic pathways (122). Furthermore, their capacity to serve as biocompatible, targeted drug-delivery vehicles enhances therapeutic specificity while minimizing systemic toxicity (122).

Despite these promising advances, the clinical translation of exercise-induced EVs remains in its infancy. Major challenges include the standardization of isolation and purification protocols, validation of biosafety and reproducibility and identification of optimal sources, dosages and delivery routes. Bridging the translational gap will require rigorous mechanistic studies and well-designed clinical trials. Interdisciplinary collaboration among scientists in biology, medicine and exercise science will be essential to elucidate the molecular underpinnings of EV-mediated effects and to refine their therapeutic applications.

While most studies emphasize the beneficial roles of exercise-induced EVs, the potential for adverse or maladaptive effects cannot be entirely ruled out. To date, no direct adverse outcomes have been associated with exosome release during exercise; however, under extreme or pathological conditions, such as overtraining, acute oxidative stress or underlying metabolic disorders, the molecular composition of EV cargo may shift toward a pro-inflammatory or stress-related profile (26,123). These alterations may transiently influence endothelial or immune cell function, reflecting physiological stress responses rather than overt toxicity. Such findings highlight the need to investigate dose-response relationships, thresholds of exercise intensity and the temporal patterns of EV secretion, in order to better differentiate between adaptive and maladaptive physiological outcomes.

In summary, exercise-induced EVs represent a dynamic and rapidly evolving frontier in translational medicine, with marked potential as next-generation therapeutic agents for health optimization and disease intervention. Continued investigation of their biological roles, together with advances in EV engineering and application technologies, will accelerate their incorporation into precision medicine and foster transformative innovations in healthcare.

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## Availability of data and materials

Not applicable.

## Authors' contributions

ZLW conducted comprehensive literature collection and organization, designed the structure of the review, drafted the original manuscript, integrated the literature and completed all revisions of the manuscript. WJG participated in drafting and organizing the original manuscript and contributed to subsequent revisions. HJH contributed to literature collection and content organization, participated in drafting and integrating key mechanistic sections of the initial manuscript, prepared schematic figures and data visualizations, and contributed to subsequent revisions of the manuscript. YZ contributed to methodology development and participated in drafting and revising the original manuscript. NL supervised the study, contributed to conceptualization and project administration, participated in refinement of the initial manuscript, and revised the manuscript critically for important intellectual content. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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