Effects of exercise-derived extracellular vesicles: Epigenetic regulatory mechanisms and protective roles (Review)

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Abstract. Exercise exerts broad and sustained effects on metabolic homeostasis and overall physiology. However, the circulating mediators connecting localized exercise responses to coordinated systemic adaptation remain poorly defined, particularly those involved in inter-organ communication and long-term metabolic remodeling. Extracellular vesicles (EVs) have gained significant attention as key mediators in this signaling process, owing to their ability to transport proteins, metabolites, and RNAs between donor and recipient cells. Exercise dynamically modulates EV release, abundance, and cargo composition, suggesting that EVs may act as key mediators of exercise-induced multisystem adaptation. Notably, exercise may alter the epigenetically active cargo of EVs, regulating epigenetic responses in target organs and ultimately shaping systemic metabolic homeostasis. Given the potential importance of these mechanisms in the long-term systemic effects of exercise, a comprehensive review of the current evidence is essential. In the present review EV-mediated epigenetic signaling in exercise is investigated, focusing on how exercise reshapes EV biogenesis and cargo composition, how EV-associated epigenetic factors regulate recipient-cell function, and how these processes may contribute to sustained metabolic adaptation. This perspective aims to clarify the mechanistic basis of exercise benefits and to highlight EVs as potential targets for precision diagnostics and therapeutic strategies.

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Abbreviations: JNK2, c-Jun N-terminal kinase 2; EMVs, endothelial-derived microvesicles; EPC, endothelial progenitor cell; EVs, extracellular vesicles; HSP, heat shock protein; IGF-1, insulin-like growth factor-1; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; miRNA or miR, microRNA; MISEV, Minimal Information for Studies of Extracellular Vesicles; MMP9, matrix metalloproteinase 9; MPCs, myogenic progenitor cells; MVBs, multivesicular bodies; MVs, microvesicles; myomiRs, muscle-specific microRNAs; ncRNA, non-coding RNA; PMVs, platelet-derived microvesicles; Treg, regulatory T cell

Key words: exercise, extracellular vesicle, epigenetic regulation, miRNA

Contents

1. Introduction

Regular exercise is essential for maintaining systemic metabolic homeostasis and overall health, reducing disease susceptibility, and improving long-term health outcomes (1-5). Reflecting these wide-ranging and sustained benefits, the World Health Organization has identified the promotion of exercise at the population level as a global public health priority (6). Structured exercise and lifestyle interventions yield measurable clinical benefits, particularly in high-risk populations. Previous studies within the LIGHT trial framework suggest that digital health-supported programs are associated with reduced atherosclerotic cardiovascular disease risk estimates and improved peak VO_2, underscoring the clinical significance of exercise-induced systemic adaptation (7,8). However, the molecular mechanisms underlying these adaptations remain inadequately defined, including the circulating mediators that coordinate inter-organ signaling and the downstream pathways that support durable metabolic reprogramming (9,10). Defining these signaling mechanisms is essential to mechanistically linking local tissue responses to coordinated systemic adaptations and durable metabolic benefits.

Exercise induces profound changes in the systemic landscape, characterized by the influx of exercise-responsive nucleic acids, proteins, and metabolites into the circulation (11,12). These exercise-induced signals provide a molecular

basis for the coordinated multi-organ response to exercise and are increasingly recognized as key drivers of the transition from short-term physiological regulation to long-term metabolic adaptation (13-15). Numerous exercise-induced signals are intrinsically unstable and lack canonical secretion motifs, making them unlikely to mediate long-range effects through passive diffusion alone. Consequently, extracellular vesicles (EVs) have emerged as important candidates for the transmission of exercise-related signals (16-18). EVs are lipid bilayer-enclosed vesicles released by nucleated cells that can carry donor cell-derived bioactive cargo, including metabolites, proteins, and RNA, to recipient cells, mediating targeted intercellular and inter-organ communication (19-22). However, the terminology used in exercise-EV studies remains variable, partly because vesicles are classified according to different criteria, including biogenesis, size, cellular origin, and isolation or characterization strategy (23,24). Thus, labels such as exosomes, small EVs, and microvesicles may describe overlapping but not necessarily identical vesicle populations across studies, with exosomes generally referring to vesicles of endosomal origin, microvesicles to vesicles shed from the plasma membrane, and small EVs to size-defined vesicle fractions (25). To avoid overclassification, the present review uses EVs as the overarching term and retains subtype-specific terminology when supported by the original reports. Although accumulating evidence indicates that exercise markedly alters EV abundance and molecular features, the precise role of these changes in mediating exercise-related biological effects remains poorly understood (26,27).

Among the potential mechanisms, epigenetic regulation is particularly well-suited to explain the enduring effects of exercise adaptation as it allows environmental cues to drive stable yet reversible changes in gene expression (28-30). Epigenetic regulation encompasses DNA methylation, histone post-translational modifications, and non-coding RNA (ncRNA)-mediated regulatory processes, all of which modulate chromatin state and gene expression without altering the underlying DNA sequence itself (31). Crucially, EVs can deliver epigenetically relevant cargo, particularly ncRNAs, to recipient cells, thereby providing a means for epigenetic regulation across tissues (32). Although EV-mediated effects may extend beyond microRNAs (miRNAs or miRs) to other classes of ncRNAs, including long non-coding RNAs and circular RNAs, and downstream chromatin-related regulation, direct evidence for these mechanisms in the exercise setting remains limited. By contrast, the strongest and most consistent evidence to date centers on EV-associated miRNAs, which therefore constitute the primary mechanistic focus of the present review (33,34). Substantial evidence indicates that EVs regulate diverse physiological and pathological processes, including metabolic homeostasis and inflammatory responses, and influence disease progression through the delivery of ncRNAs (35). Exercise, in turn, dynamically modulates EV release and cargo composition, thereby reshaping EV-mediated epigenetic regulation (36-38).

EVs have attracted broad translational interest as minimally invasive biomarkers and potential delivery-based therapeutic platforms, owing to their stability in biofluids and their capacity to carry protected molecular cargo (39-41). In the exercise field, changes in EV abundance, surface-marker profiles, and miRNA cargo have been associated with acute exercise responses, fatigue-related physiological stress, metabolic health, and training responsiveness (42-44). Therapeutic translation remains less established, with current evidence largely derived from preclinical studies suggesting that exercise-induced EVs or exercise-regulated cargo can modulate inflammation, tissue repair, cardiometabolic remodeling, and organ protection (45). However, the mechanisms governing the selection, delivery, and tissue-specific coupling of exercise-responsive EV cargo to epigenetic remodeling and downstream metabolic adaptation remain poorly defined. A systematic synthesis of current evidence is therefore needed to clarify how EV-mediated epigenetic signaling links exercise to sustained, multisystem metabolic benefits.

2. EVs: An intrinsic carrier for molecular protection and directed delivery

In 1967, Peter Wolf described platelet-derived 'platelet dust' in plasma, marking one of the earliest reports of circulating EVs (46). Initially considered waste disposal by-products, these vesicles are now recognized as functional mediators of intercellular communication (11,47). To standardize terminology, the International Society for Extracellular Vesicles proposed in 2018 that 'extracellular vesicles' should be used as the generic term for particles naturally released from cells (48). EVs are nanoscale, lipid bilayer-enclosed vesicles that transfer lipids, nucleic acids, proteins, and other biomolecules to nearby or distant recipient cells, thereby mediating intercellular communication (49). This EV-mediated communication pathway is evolutionarily conserved across prokaryotes, plants, and eukaryotes, including yeast and fungi (50). Based on their biogenesis, EVs are broadly divided into exosomes and plasma membrane-derived vesicles (51). Exosomes, typically within the small EV size range (30-150 nm), originate from the endocytic pathway as intraluminal vesicles within multivesicular bodies (MVBs) and are released when MVBs fuse with the plasma membrane. They are often enriched in CD9, CD63, CD81, ALG-2-interacting protein X, heat shock protein (HSP)70, and tumor susceptibility 101 (52,53). By contrast, plasma membrane-derived vesicles bud directly from the cell surface and include microvesicles (MVs, typically 501,000 nm) and apoptotic vesicles (100-5,000 nm), the latter being generated during apoptosis (54). After release, EVs may enter circulating biofluids, distribute locally or systemically, and reach distant recipient cells, enabling communication across both proximal and remote sites (39). Some EVs rapidly degrade after release, directly releasing cytokines or growth factors, whereas most remain stable in biofluids and can travel to specific tissues or distant target cells (11). Upon reaching target cells, EVs interact through three primary mechanisms: Receptor binding at the cell surface, direct membrane fusion, or endocytic uptake (55). The uptake of EVs varies by cell type and is largely governed by their surface protein composition, especially integrins, tetraspanins, and lectins (51). Additionally, EV cargo loading is increasingly recognized as a selective process, not a purely passive one. It involves mechanisms such as endosomal sorting complex required for transport (ESCRT)-dependent and ESCRT-independent pathways, lipid microdomain-associated processes, and RNA-binding protein-mediated loading of

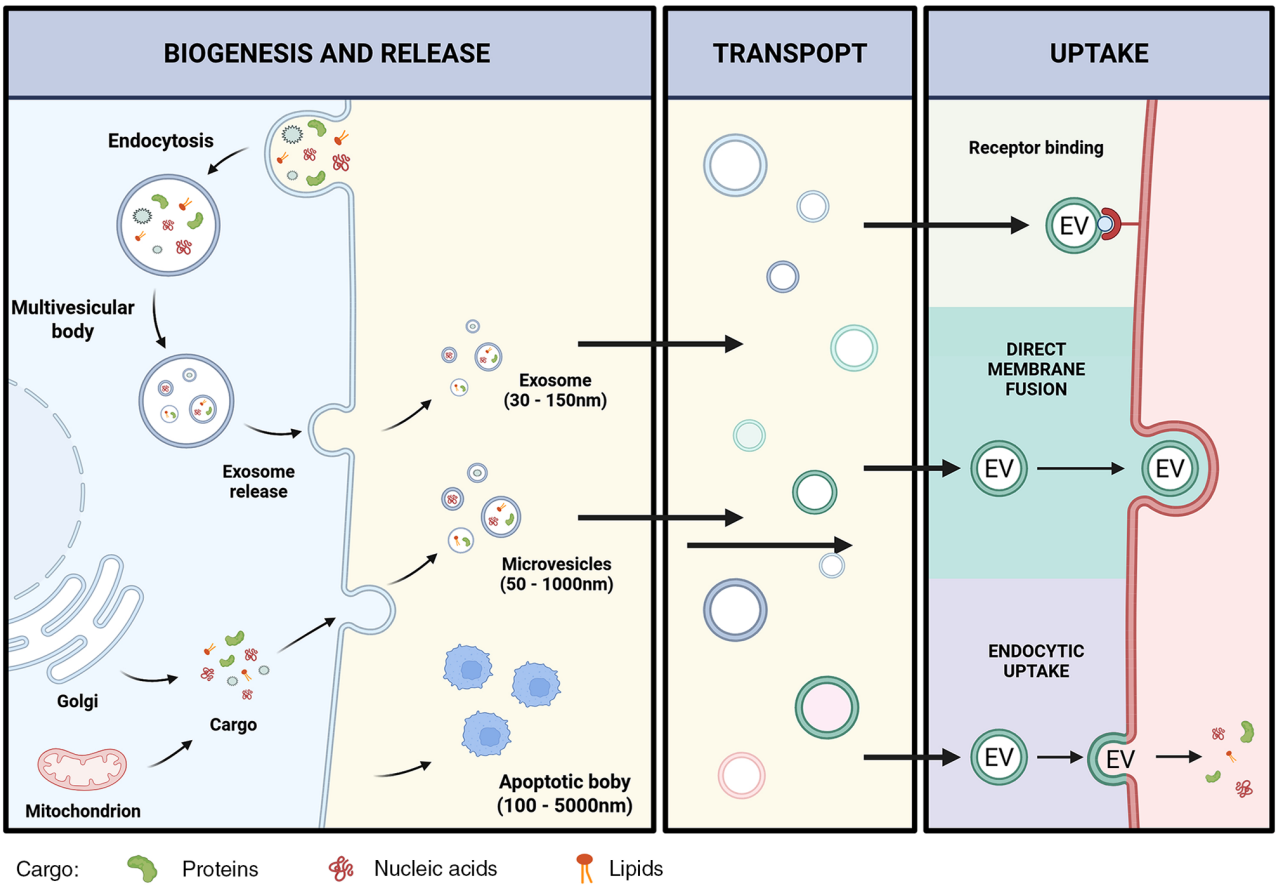

Figure 1. Biogenesis, release, transport, and uptake of EVs. EVs are generated through distinct biogenetic routes and carry bioactive cargo, including proteins, nucleic acids, and lipids. Exosomes are formed through the endosomal pathway: Endocytosis generates early endosomal compartments, which mature into MVBs containing intraluminal vesicles; fusion of MVBs with the plasma membrane releases these vesicles as exosomes, typically within the small EV size range. Microvesicles are produced by direct outward budding of the plasma membrane, whereas apoptotic bodies are released during apoptosis. After release, EVs can travel through extracellular fluids or the circulation and deliver donor cell-derived signals to recipient cells. EV uptake may occur through receptor binding at the cell surface, direct membrane fusion, or endocytic internalization, thereby enabling transfer of molecular cargo and contributing to intercellular and inter-organ communication. EVs, extracellular vesicles; MVBs, multivesicular bodies.

regulatory RNAs (56,57). This selective packaging further contributes to the molecular composition and functional specificity of EVs, influencing which regulatory signals are delivered to recipient cells (58,59).

Taken together, EVs should not be viewed as passive released cellular debris, but as active biological carriers that protect bioactive molecules from degradation and enable their selective delivery to recipient cells, thereby supporting intercellular and inter-organ communication (Fig. 1).

3. Cellular origins of exercise-induced EVs

As a systemic physiological stimulus, exercise reshapes circulating EV profiles by altering both EV release and cargo composition (37,60). While skeletal muscle is widely recognized as a major source of exercise-induced EVs, current evidence suggests that circulating EVs also originate from a broader range of cell types, including endothelial cells, platelets, and leukocytes, in response to both acute or chronic exercise (61-64). Notably, despite the marked plasticity of circulating EV signals, EVs from distinct tissue origins often retain relatively stable source-associated features (65) (Table I). These origin-dependent characteristics largely determine their surface molecular identity, cargo profile, tissue tropism, and cellular uptake efficiency, thereby influencing downstream signaling, transcriptional programs, and metabolic reprogramming in recipient cells, and ultimately shaping their functional effects in target organs (66). Accordingly, a systematic understanding of how exercise regulates EVs derived from different cellular sources is essential not only for elucidating the systemic adaptations to physical activity, but also for defining the physiological functions of EVs and their potential diagnostic and therapeutic value.

Skeletal muscle-derived EVs. Skeletal muscle, comprising 35-40% of body mass, functions as both a primary motor effector and a critical endocrine organ. Beyond myokine secretion, emerging evidence indicates that skeletal muscle also releases bioactive EVs, mediating complex intercellular and inter-organ communication (67). Guescini *et al* (68) were the first to show that myoblasts release exosome-like vesicles (50-80 nm) enriched in signaling-related proteins and mitochondrial DNA, suggesting their role in transferring genetic and metabolic information between muscle cells and potentially across organs. This view was further supported by the detection of fluorescently labeled EVs in distant, including contralateral,

Table I. Major cellular sources and defining features of exercise-related EVs.

EV origin	Specific cargo	Exercise response	Major biological function	Surface markers
Skeletal muscle	miR-1, miR-133a/b, miR-206, miR-486, miR-499	Dynamically remodeled by exercise mode, intensity, duration, and training status	Mediate local myofiber communication and long-range inter-organ signaling; contribute to myogenesis, regeneration, metabolic adaptation, insulin sensitivity, and systemic homeostasis	SGCA, CD81
Platelets	Platelet activation-related proteins, membrane lipids, procoagulant and signaling molecules	Rapidly increased after acute high-intensity exercise; transient and intensity-dependent	Reflect platelet activation, acute physiological stress, and vascular-hemostatic responses; may participate in coagulation, inflammation, and post-exercise vascular adaptation	CD41, CD42, CD31
Endothelial cells	Endothelial activation- or injury-related proteins, adhesion molecules, and regulatory nucleic acids	Variable responses depending on exercise protocol, fitness level, and study method	Reflect endothelial activation, vascular stress, and vascular fitness; may serve as indicators of endothelial adaptation to exercise	CD144, CD62E, CD105, CD146
Regulatory T cells	miR-150-5p, miR-146a-5p, miR-21-5p	Altered with exercise-induced immune activation	Involved in immune cell communication, inflammatory regulation, and exercise-associated immune adaptation	CD45, CD11b, CD14, CD16

EV, extracellular vesicle; miR, microRNA; SGCA, α-sarcoglycan; CD, cluster of differentiation.

muscles after intramuscular injection (69). *In vitro* and animal studies further indicate that multiple skeletal muscle cell types, including myoblasts, myotubes, and satellite cells, can release exosomes enriched in muscle-specific miRNAs (myomiRs) such as miR-1, miR-133a/b, miR-206, and miR-486 (70,71). These myomiRs, which are highly enriched in muscle tissue, play important roles in myogenesis, differentiation, regeneration, and stress responses (61,72).

Exercise can markedly alter both the abundance and molecular cargo of circulating exosomes, in a manner that depends on exercise modality, intensity, and host-related factors (61). Different forms of exercise, including uphill running, downhill running, endurance training, and resistance training, induce distinct changes in exosomal miRNA expression patterns, with dynamic fluctuations in molecules such as miR-1, miR-133a, miR-499, and miR-486 (73). Among these, miR-486 can target PTEN and thereby enhance insulin-like growth factor-1/protein kinase B/mechanistic target of rapamycin (IGF-1/AKT/mTOR) signaling, suggesting that exercise-induced exosomal miRNAs may contribute to protein synthesis, glucose homeostasis, and improved insulin sensitivity (74). On the basis of these findings, skeletal muscle is now considered a major source of circulating exosomes.

Functionally, muscle-derived EVs help maintain local tissue homeostasis by promoting myoblast differentiation, supporting neuromuscular junction integrity, and protecting motor neurons (75). They can also reach distant metabolic organs, where they influence signaling pathways involved in insulin responsiveness, glucose handling, lipid metabolism, and systemic metabolic homeostasis (76-79). Altered muscle exosomal cargo has been linked to both pathological and adaptive responses in neuromuscular and metabolic diseases, highlighting the potential of muscle-derived EVs as biomarkers and therapeutic targets (80-84).

Platelet-derived EVs. A substantial proportion of human studies investigating the effects of acute exercise on circulating EVs have focused on larger vesicle populations, particularly MVs exceeding 500 nm in diameter (27). Among these, platelet-derived microvesicles (PMVs) represent the most abundant MV subset in circulation and have attracted significant attention due to their robust responsiveness to exercise (85-87). Across a range of high-intensity endurance modalities, including maximal incremental exercise testing, heavy-intensity cycling, sustained aerobic exercise near 70-85% of maximal capacity, and high-intensity interval protocols, PMVs consistently exhibit marked increases during or shortly after exercise (88-91). Notably, these changes appear to be intensity dependent, as moderate-intensity exercise does not elicit comparable elevations (92). Moreover, the PMV surge is transient, with concentrations peaking during exercise or early recovery and returning toward baseline within 30-120 min (85,86,92). Together, these findings highlight PMVs as dynamically regulated vesicles that may reflect acute physiological stress and vascular activation during strenuous exercise.

Endothelial cell-derived EVs. Compared with PMVs, the exercise-induced behavior of endothelial-derived microvesicles (EMVs) is less consistent. While several studies have demonstrated post-exercise elevations in EMVs (91,93), others have reported no change or even reductions, both in healthy

and metabolically compromised individuals (85,89,94). These discrepancies likely reflect methodological variability in EV isolation and characterization, as well as differences in exercise intensity, modality, and participant characteristics. Notably, emerging evidence suggests that training status may critically shape EMV dynamics. In highly trained endurance athletes, distinct heavy-intensity exercise formats, including prolonged submaximal workloads, repeated high-intensity intervals, and maximal sprinting, were uniformly associated with reductions in circulating EMVs, potentially reflecting enhanced vascular function and accelerated vesicle clearance in trained individuals (95,96). These observations underscore that EMV responses are not uniform and may integrate information about both exercise stimulus and vascular fitness.

Regulatory T cell-derived EVs (Treg-EV). Treg-EVs primarily carry a range of immunosuppressive molecules and miRNAs that contribute to the maintenance of immune tolerance and the suppression of inflammatory responses (74). They are enriched in molecules such as CD39, CD73, cytotoxic T-lymphocyte-associated protein 4, IL-35 subunits, IL-10, and TGF-β, as well as regulatory miRNAs including miR-150-5p, miR-146a-5p, and miR-21-5p (76,97-99). Among these, miR-146a-5p has been shown to suppress $CD4^+$ T-cell proliferation, further supporting the immunoregulatory function of Treg-EVs (100). During exercise, Treg-EVs may exert immunomodulatory effects through these molecular cargos, attenuating inflammatory responses and fostering an anti-inflammatory milieu, particularly in chronic metabolic disorders such as diabetes and obesity, as well as during recovery from exercise-induced muscle injury (100). Notably, Treg cells may act in concert with skeletal muscle-derived EVs to coordinate post-exercise immune adaptation and tissue repair (62,101). For example, muscle-derived EVs may enhance Treg activation and immunosuppressive function through miRNAs such as miR-206, amplifying anti-inflammatory signals via EV-mediated communication (102). Simultaneously, Treg-EVs may suppress excessive immune-cell responses and reinforce immune tolerance through the delivery of miR-146a-5p (103). In this cooperative framework, EVs, through their carried cargo, may serve dual roles in regulating immune responses and promoting both metabolic health and tissue repair.

4. Exercise-driven changes in EV composition and function

Exercise, including acute and chronic exercise, refers to voluntary movements produced by skeletal muscles that elevate energy expenditure (104,105). In response to the increased physiological demands of exercise, the body engages coordinated adaptations across metabolic, cardiovascular, and immune systems, collectively underpinning the broad and sustained health benefits of regular physical activity (106-109). In 2015, Frühbeis *et al* (110) were the first to systematically document the rapid changes in circulating EVs following acute exercise, identifying EVs as potential mediators of exercise-induced inter-organ communication. By transporting proteins, lipids, and regulatory RNAs through the circulation, EVs can relay local signals generated by contracting skeletal muscle to distant tissues, including the vasculature, liver, adipose tissue, and immune system, thereby linking muscle activity to systemic adaptation (111-113). Recent studies indicate that EV responses vary substantially across different exercise modalities. Acute vs. chronic exercise, along with variations in intensity and duration, each reshape EV abundance, cellular origin, and cargo composition in distinct ways (114-116). For example, short bouts of cycling are associated with increased exosomal miR-1, whereas longer-duration exercise induces a broader myomiR response, including miR-1, miR-133a/b, miR-206, miR-208a, and miR-499 (73,117,118). The present review synthesizes recent evidence on the dynamic behavior of EVs across different forms of exercise, particularly endurance and resistance training, offering a clearer framework for understanding the mechanisms of exercise adaptation (Table II).

Acute exercise-induced changes in EVs. Acute exercise refers to a single bout of short-duration physical activity, typically lasting from several minutes to a few hours (119,120). Unlike the chronic adaptations associated with long-term training, acute exercise primarily represents a rapid physiological response to transient physical stress that can quickly reconfigure multisystem homeostasis and confer immediate health benefits (121-123). Even a single acute exercise bout can acutely improve systemic metabolic status, enhance insulin sensitivity, and promote energy utilization in major metabolic organs such as skeletal muscle and the liver (124-126). In addition, acute exercise exerts both anti-inflammatory and immune-activating effects, providing a brief but efficient form of endogenous protection through improved endothelial function and redistribution of immune cell populations (127,128).

A substantial body of human evidence consistently shows that acute exercise is a potent stimulus for the transient elevation of circulating EVs (129). Early exploratory research used graded cycling or treadmill tests to impose acute physiological stress in healthy, physically active men and assessed plasma small EV kinetics after isolation by differential centrifugation and ultracentrifugation (100,000 x g). This research showed that acute exercise rapidly increases circulating small EV levels: In cycling protocols, particle concentrations rose by approximately 2- to 3-fold and exosomal marker proteins by ~5-fold, peaking immediately after exercise and returning to baseline within 90 min of recovery (110). Notably, EV release occurred before the anaerobic threshold and exhibited rapid release-and-clearance kinetics, supporting a role for EVs as immediate physiological signaling mediators rather than passive by-products of tissue damage (110).

A parallel study of healthy men highlights a distinct kinetic divergence between exercise paradigms: While cycling triggered a sharp, transient peak in EV abundance, an incremental treadmill test resulted in a more moderate (~1.5-fold) elevation in circulating small EVs, which remained elevated for 90 min and required 6 h to return to baseline (130). Animal models further corroborate these dynamics. In Wistar rats, acute treadmill running significantly enhanced serum EV concentrations and protein content without a concomitant surge in total small-RNA yield (131). These findings suggest that the exercise-induced signal resides not in the sheer abundance of RNA, but in the selective remodeling of the molecular cargo. Deep sequencing has identified 12 differentially expressed miRNAs following exercise, whose targets predominantly

Table II. Exercise-induced alterations in circulating EVs.

Exercise protocol		Bio-fluid	Time of collection	Isolation method	Verification method	Terminology	Exercise effect	Year	(Refs.)
Acute exercise	Incremental cycling or treadmill running to exhaustion in healthy adults	Plasma	Pre-exercise, immediately post-exercise, and 90 min post-exercise	Differential centrifugation, including 10,000 x g pre-clearing, filtration, and 100,000 x g ultracentrifugation	NTA and WB	Small EVs/ exosome-like vesicles	Small EVs increased immediately after cycling and declined by 90 min; the running response was more moderate but appeared more sustained	2015	(110)
	Incremental cycling test to exhaustion in healthy male athletes	EDTA plasma	Pre-exercise, during exercise (RQ=0.9), and immediately post-exercise	EV Array on total plasma; SEC; CD9/CD63/CD81 immunobead isolation	EV Array, NTA, WB, and multiplex flow cytometry	EVs	EV levels increased progressively during exercise and peaked at maximal load; ExerVs showed mixed leukocyte-, platelet-, and endothelial-associated features	2019	(132)
	Single 40-min treadmill bout (low-, moderate-, or high-intensity) in rats	Serum	Immediately after the exercise bout	ExoQuick-based precipitation from platelet-depleted serum	TEM/immuno-EM, TRPS, and WB	EVs	EV concentration increased, whereas size was not significantly changed; CD63-positive vesicles increased and small-RNA cargo was altered	2018	(131)
	Moderate-intensity treadmill exercise (60% VO_2max) in obese and normal-weight adults	Plasma	Pre-exercise, immediately post-exercise, 3 h, and 24 h	Plasma EV isolation/purification (supplementary protocol), followed by NTA and flow-based phenotyping	NTA and flow cytometry	Total EVs, exosomes, and microvesicles	Total circulating EVs decreased overall (mainly microvesicle-range EVs); $CD61^+$ EVs decreased,whereas $SGCA^+$ EVs increased; responses were sex- and BMI-dependent	2020	(133)
	60-min cycling in healthy men (30 min at 55%, 20 min at 70%, then ~10 min at 80% VO_2max to exhaustion), with 4-h recovery	Plasma	Baseline, end of exercise, and 4 h recovery	Rapid plasma preparation followed by high-speed centrifugation to obtain a 20,000 x g EV fraction for proteomics	NTA, cryo-EM, and nano-UHPLC-MS/MS proteomics	EVs, exosomes, and small vesicles	Exercise increased systemic release of EV-associated proteins and enriched exosome/small-vesicle signatures; exercise-liberate	2018	(26)

Table II. Continued.

Exercise protocol		Bio-fluid	Time of collection	Isolation method	Verification method	Terminology	Exercise effect	Year	(Refs.)
	Clinical exercise stress testing in human subjects	EDTA plasma	At rest, peak exercise, and 15 min after exercise	Plasma preparation by sequential centrifugation; direct particle analysis by nano-flow cytometry	Nano-flow cytometry	EVs/plasma EVs	Acute exercise induced a rapid increase in circulating plasma EVs	2017	(44)
Chronic exercise	3-week swimming in mice	Serum	After completion of the training period	Plasma EV isolation followed by size and phenotyping analyses	Nano-flow cytometry	EVs/serum EVs	Serum EVs were increased (~1.85-fold) after training	2017	(44)
	Daily moderate treadmill exercise (20 min/day for 2 weeks) in rats	Serum	1 h and 18 h after the last exercise session	Precipitation-based isolation (miRCURY Exosome Isolation Kit)	Marker assays and biochemical profiling	EVs/exosomes	Exercise produced delayed changes in circulating EV profile, with alterations more evident 18 h after the last session	2018	(146)
	4-week swim training in rats/trained human volunteers	Plasma	24 h after the last training session	Differential ultracentrifugation; ExoQuick also used	Exosome characterizati on plus functional assays	Circulating exosomes/plasma exosomes	Total circulating exosome level did not change significantly 24 h post-exercise, but cargo composition/function was altered	2019	(45)
	4-week treadmill training (low vs. moderate intensity; 60 min/ day, 5 days/week) in mice	Plasma	24 h after the last bout of exercise	Microbead-based sorting of circulating EPC-derived exosomes	NTA, WB qPCR ,	Exosomes/EPC-derived exosomes	Exercise increased circulating EPC-derived exosome release in an intensity-dependent manner	2018	(150)

EVs, extracellular vesicles; EDTA, ethylenediaminetetraacetic acid; NTA, nanoparticle tracking analysis; WB, western blotting; TEM, transmission electron microscopy; TRPS, tunable resistive pulse sensing; SEC, size-exclusion chromatography; RQ, respiratory quotient; SGCA, α-sarcoglycan; EPC, endothelial progenitor cell; qPCR, quantitative polymerase chain reaction.

converge on the MAPK signaling pathway (131). These data indicate that acute aerobic exercise rapidly reshapes both the physical abundance and the molecular signature of circulating EVs, positioning them as precise mediators of immediate inter-organ signaling.

The cellular origins of acute exercise-induced EVs are highly context-dependent. In healthy men performing a fasting, graded cycling-to-exhaustion test, EV-associated signals progressively increased during exercise peaking at exhaustion. Under these acute exhaustive conditions, exercise-induced EVs predominantly originated from lymphocytes, monocytes, endothelial cells, and platelets, with no significant contribution from skeletal muscle-derived EVs (132). By contrast, research using moderate-intensity exercise revealed a different pattern. In sex-stratified cohorts of both obese and normal-weight individuals, acute treadmill exercise (~60% VO_2max) rapidly reshaped the circulating EV landscape. Skeletal muscle-derived α-sarcoglycan $(SGCA)^+$ EVs increased immediately after exercise, whereas platelet-derived $CD61^+$ EVs declined during recovery, particularly at 24 h (133). These responses also varied by sex and metabolic status: Women showed higher MV but lower exosome levels, and normal-weight individuals exhibited a stronger MV response than obese participants (133). Consistent with this, additional research has demonstrated marked sex differences in exercise-induced microparticle responses, with men showing post-exercise increases in $CD62E^+$ endothelial microparticles, while women showed a more pronounced rise in $CD34^+$ microparticles (91). Together, these findings indicate that the source composition of exercise-induced EVs is shaped not only by exercise intensity and modality, but also by sex and metabolic state.

Beyond changes in abundance and cellular origin, acute exercise also reshapes EV function. In healthy men undergoing incremental cycling, Whitham *et al* (26) showed that acute exercise induces a marked but transient remodeling of the circulating EV proteome, with 322 proteins significantly altered immediately after exercise and most changes largely resolving within 4 h. Upregulated proteins were enriched in pathways related to vesicle biogenesis, membrane trafficking, adhesion, cytoskeletal remodeling, and signal transduction, highlighting a rapid activation of EV-associated signaling machinery (26). Notably, exercise-derived EVs showed greater hepatic accumulation than resting EVs and were capable of transferring protein cargo to hepatocytes, supporting their role as active mediators linking contracting tissues to metabolic organs rather than passive by-products of exercise (26). The functional relevance of exercise-induced EVs extends to vascular biology. In healthy men, vigorous acute exercise rapidly increased circulating endothelial-derived microparticles, and phenotypic analysis indicated that these vesicles primarily reflected endothelial activation rather than overt endothelial apoptosis (94). This suggests that acute exercise-induced EV release is more closely associated with adaptive endothelial stress signaling than with widespread vascular injury. Accordingly, circulating EVs may serve not only as sensitive indicators of exercise stress, but also as early effectors of vascular repair, endothelial regulation, and exercise-induced cardiovascular protection.

Although still limited, current *in vivo* evidence strongly supports a functional role for EVs in mediating the cross-organ protective effects of acute physical activity. Acute exercise rapidly increases circulating EVs, many of which are predominantly derived from activated platelets and endothelial cells, while simultaneously remodeling their cargo, including proteins, miRNAs, and metabolites. By carrying these exercise-responsive signals through the circulation, EVs may coordinate multiorgan metabolic adaptation and functional integration through epigenetic regulation and the modulation of key signaling pathways.

Chronic exercise-induced changes in EVs. Chronic exercise refers to regular physical activity performed over an extended period (134,135). Unlike the transient physiological stress triggered by a single bout of acute exercise, chronic exercise is characterized by repeated exercise stimuli that drive durable functional adaptation and structural remodeling, resulting in broad, long-lasting, and systemic health benefits (136-138). Long-term exercise training substantially lowers the risk of multiple non-communicable diseases, including metabolic disorders (such as obesity and type 2 diabetes), cardiovascular disease, cancer, and neurodegenerative conditions (134,136,139,140). Through long-term physiological regulation, chronic exercise reshapes systemic metabolic homeostasis, supports more efficient energy utilization and insulin sensitivity, delays biological aging, and ultimately extends healthspan (141-143). In addition, by improving the overall immune microenvironment, chronic exercise enhances long-term host defense against pathogen exposure (144,145).

At the molecular level, in contrast to the rapid post-exercise rise in circulating small EVs observed after acute exercise, the effects of chronic exercise training on circulating EVs appear to be more consistent with a delayed, homeostatic form of remodeling (27). In a study of Wistar rats across different age groups, Bertoldi *et al* (146) applied a 2-week moderate-intensity treadmill training protocol (20 min/day, ~60% VO_2max) and collected blood at 1 h and 18 h after the final session. Training-related effects were observed mainly at the 18-h time point, suggesting that regular aerobic exercise may promote exosome release or increase circulating exosome-associated components in a delayed manner (146). In aged animals, elevated EV-associated acetylcholinesterase activity was reduced after training, indicating that chronic exercise may also partially correct aging-associated EV abnormalities. Notably, this study also identified time-of-day differences in CD63 measurements (afternoon vs. the following morning), underscoring the importance of strict control of sampling time and circadian factors in studies of chronic exercise and EV biology (146). Overall, these findings suggest that chronic exercise contributes to sustained systemic protection, at least in part, by remodeling the quantitative profile of circulating EVs.

Further evidence for the organ-protective effects of exercise-derived EVs comes from chronic training models. In a 3-week swimming-trained mouse model, Bei *et al* (44) showed that chronic endurance exercise increased circulating EV abundance and, more importantly, that the transfer of EVs from exercised mice reduced ischemic myocardial injury, suppressed cardiomyocyte apoptosis, and improved cardiac function in recipient animals (44). Similar protective

effects were observed *in vitro*, where exercise-derived EVs enhanced cardiomyocyte survival and attenuated apoptotic signaling. These actions were closely linked to activation of ERK1/2-HSP27 signaling, supporting the view that exercise-induced EVs are not merely by-products of training, but active effectors of remote organ protection and post-stress tissue recovery. When sampling time is carefully controlled, however, the effects of chronic training on circulating exosome levels appear more nuanced. In trained young male rowers and swim-trained rats, plasma exosome size and concentration were unchanged 24 h after the final exercise bout, yet exosomes from trained subjects displayed enhanced cardioprotective activity (137). Specifically, these exosomes were more readily taken up by cardiomyocytes, reduced hypoxia/reoxygenation injury *in vitro*, and attenuated ischemia-reperfusion damage *in vivo*. This functional remodeling was linked to enrichment of miR-342-5p, which inhibits caspase-9/c-Jun N-terminal kinase 2(Caspase9/JNK2)-dependent apoptosis and enhances AKT-mediated survival signaling (137). More broadly, chronic exercise appears to promote long-term adaptation and disease protection by selectively remodeling the cargo of EVs from different tissues. In *db*/*db* mice, 8 weeks of treadmill training increased exosome release and elevated miR-455 and miR-29b, thereby attenuating diabetic myocardial remodeling through suppression of matrix metalloproteinase 9 (MMP9) (147). A recent human study further extends these observations to metabolic disease settings. In individuals with insulin resistance or type 2 diabetes, 12 weeks of high-intensity interval training followed by detraining was associated with partially sustained improvements in energy metabolism and hepatic insulin sensitivity, raising the possibility that small EV remodeling contributes to the persistence of some exercise-induced metabolic benefits (148). Similarly, a study in sedentary adults with obesity showed that endurance training significantly remodeled the circulating EV proteome and reduced systemic inflammation, even without marked changes in EV abundance (149). Together, these findings suggest that, under metabolically compromised conditions, exercise may reprogram EV function not only by altering vesicle levels, but also by reshaping EV cargo and signaling properties (149). Chronic exercise has also been shown to enhance vascular repair through endothelial progenitor cell (EPC)-derived EVs: 4 weeks of treadmill training increased circulating EPCs, boosted EPC exosome release and miR-126 content, and promoted adaptive vascular remodeling via the sprouty-related EVH1 domain-containing 1/vasular endothelial growth factor axis (150). In addition to RNA cargo, chronic exercise may also remodel EV-associated proteins, as suggested by increased skeletal muscle HSP60 after endurance training, raising the possibility that EV-associated protein signals contribute to systemic adaptation (151).

Taken together, current evidence supports a central role for EVs in mediating the long-term benefits of chronic exercise. Rather than simply increasing circulating EV levels, chronic exercise appears to induce a more stable functional reprogramming of EV cargo, enabling sustained miRNA- and protein-mediated signaling that may reinforce epigenetic remodeling, metabolic adaptation, and systemic homeostasis.

5. Exercise-induced EVs as mediators of epigenetic remodeling

Exercise-induced changes in EVs are likely to be functionally important because they may reshape the regulatory information delivered to recipient cells (152). By altering EV abundance, subtype distribution, and cargo composition in a context-dependent manner, exercise can modify the intercellular transfer of miRNAs, proteins, metabolites, and other bioactive molecules (153). Once delivered to recipient cells, these cargos can influence signaling networks and gene programs involved in metabolism, inflammation, stress adaptation, and tissue repair (154-156). Among them, ncRNAs are especially notable, as they provide a plausible route through which exercise-responsive EVs may participate in epigenetic regulation across tissues (157). EV remodeling may therefore represent a mechanistic link between transient exercise stimuli and longer-term molecular adaptation (158). This perspective provides an important framework for considering how exercise-induced EV signaling intersects with epigenetic remodeling.

Exercise-induced epigenetic remodeling. Epigenetics refers to the dynamic regulation of gene expression through a series of plastic and reversible mechanisms that occur without altering the underlying DNA sequence (159-161). First introduced by Waddington in 1942, the concept describes how organisms establish structurally dynamic regulatory states within chromatin to precisely control transcriptional programs and adapt to environmental cues (162-164). Broadly, epigenetic regulation encompasses DNA methylation, histone post-translational modifications, chromatin remodeling, and regulation mediated by ncRNAs (165-167). These mechanisms allow external stimuli to be translated into changes in gene expression, thereby influencing metabolic homeostasis, inflammatory responses, stress adaptation, tissue repair, and disease progression (168-170). Notably, exercise can induce epigenetic reprogramming through changes in energy metabolism, redox status, and fluctuations in key metabolites such as acetyl-CoA, NAD^+, and lactate (171-173). These effects include modulation of DNA methylation at metabolism-related genes, shifts in histone acetylation and methylation, and remodeling of miRNA expression profiles, ultimately influencing mitochondrial biogenesis, fatty acid oxidation, glucose metabolism, insulin sensitivity, and inflammatory-oxidative stress responses (174-178). Because these epigenetic responses are dynamic, context-dependent, and partially persistent after training, they provide a plausible mechanistic basis for the sustained metabolic and systemic benefits of exercise (5,179-181).

Within this framework, ncRNAs, especially miRNAs, have emerged as key regulatory effectors (182-184). Exercise markedly alters miRNA profiles in both tissues and in the circulation, with these changes being increasingly linked to pathways governing metabolism, inflammation, angiogenesis, mitochondrial function, and tissue repair (185-188). Notably, a subset of miRNAs can be selectively packaged into EVs and transferred between tissues (37,189,190). This suggests that exercise-induced EV-associated miRNAs may serve as mobile epigenetic signals that connect local muscle activity to systemic adaptive remodeling (38,191,192).

Exercise-derived EVs as epigenetic messengers. Given the central roles of EVs and epigenetic regulation in exercise adaptation and metabolic health, increasing attention has recently focused on whether exercise-induced EV remodeling may function as a cross-tissue information carrier, mediating ncRNA-driven epigenetic regulation and thereby contributing to systemic metabolic benefits (193). Although this field remains in its early stages, available evidence increasingly suggests that physical activity can alter the abundance, subtype composition, and cargo profile of circulating EVs, particularly their ncRNA content, including miRNAs, and may thereby influence transcriptional programs, signaling states, and long-term adaptive remodeling in target tissues (61). To systematically evaluate the evidence on exercise-induced EV remodeling and its potential epigenetic relevance, a PubMed search was conducted using the following terms: ('exercise'[Title/Abstract] OR 'physical activity'[Title/Abstract]) AND ('extracellular vesicles'[Title/Abstract] OR 'exosomes'[Title/Abstract] OR 'EVs'[Title/Abstract]). After merging results, removing duplicates, and applying stringent screening criteria, studies were included in which exercise was the primary intervention and EVs were evaluated as mediators, biomarkers, or functional effectors, with particular emphasis on studies explicitly examining EV cargo remodeling and its roles in epigenetic regulation, inter-organ communication, or downstream transcriptional/metabolic reprogramming (Table III).

The earliest evidence for exercise-induced EV-miRNA remodeling came from studies showing that exercise alters not only the abundance of circulating EVs, but also the loading of specific miRNAs into these vesicles. Guescini *et al* (68) first identified a circulating EV subpopulation with myogenic features ($SGCA^+/CD81^+$) enriched in muscle-related miRNAs such as miR-206. They also showed that several EV-associated miRNAs were positively correlated with VO_2max at rest. After acute aerobic exercise, EV-miR-181a-5p levels significantly increased, while EV-miR-133b showed an upward trend, supporting the notion that exercise-related changes in circulating miRNAs may arise, at least in part, from active EV-mediated secretion and cargo loading rather than passive leakage from damaged tissues (68). Subsequent research reinforced this concept by showing that exercise modality influences EV-miRNA sorting. In rats, eccentric-biased downhill running, but not concentric-biased uphill running, increased multiple myomiRs in exosome-enriched fractions during early recovery. This suggests that higher mechanical strain more readily drives myomiRs into EV-associated transport pathways (73). This pattern is consistent with observations from high mechanical-load resistance exercise. After a single bout of flywheel-based inertial squats, circulating EV levels increased and EV-encapsulated miR-206 and miR-146a were selectively elevated, whereas several other miRNAs remained unchanged (194). These changes occurred alongside markers of muscle inflammation, immune activation, and recovery signaling, suggesting that EV-mediated ncRNA output may be integrated into a broader program of post-exercise stress, inflammation, and tissue remodeling. Notably, some research indicates that exercise-induced EV remodeling may be driven more by selective cargo changes than by changes in vesicle number. In untrained men subjected to a muscle-damaging exercise protocol, EV size and particle number remained unchanged, whereas EV cargo was selectively remodeled, with a significant decline in miR-31 at 24 h. Together with concurrent increases in creatine kinase and delayed-onset muscle soreness, this finding suggests that EV-mediated miRNA remodeling may contribute to post-exercise repair, potentially through satellite cell-related pathways (195). In chronic training, EV-miRNA responses appear further shaped by training status. In older men, long-term endurance training produced a stable resting exosomal miRNA signature distinct from that of sedentary controls (196). Following an acute bout of cycling, both trained and sedentary individuals exhibited exomiR remodeling, but the composition and temporal dynamics of these changes differed markedly between groups. Pathway analysis suggested that numerous exercise-responsive exosomal miRNAs target key nodes within the IGF-1/AKT/mTOR/Forkhead box O axis, with trained individuals showing a profile more consistent with IGF-1 pathway activation (196). These findings indicate that long-term training can reprogram the EV-miRNA response to acute exercise, supporting the view that EV-miRNAs may function both as molecular fingerprints of training status and as mediators of adaptive signaling.

Previous research has advanced from descriptive profiling to functional and mechanistic validation of exercise-induced EV-miRNA remodeling. In a diabetic heart model, regular exercise increased cardiac-associated EV release and remodeled their miRNA cargo, notably upregulating miR-29b and miR-455. Mechanistically, these exercise-induced EV-miRNAs, particularly miR-455, were linked to reduced MMP9 expression and activity, thereby attenuating extracellular matrix remodeling, fibrosis, and myocardial dysfunction (146). In parallel animal and human studies, Hou *et al* (45) showed that chronic exercise did not necessarily increase circulating exosome abundance 24 h after training, but substantially altered exosomal miRNA composition and function. They identified miR-342-5p as a key exercise-induced exosomal miRNA that protects against ischemia-reperfusion injury by suppressing apoptosis-related targets, including *Caspase9*, *Jnk2*, and *Ppm1f*, while enhancing AKT-dependent survival signaling. Notably, laminar shear stress also increased miR-342-5p expression in endothelial cells and their exosomes, suggesting that exercise-induced hemodynamic signals may contribute to systemic protection through an endothelial EV-miRNA pathway (45). In addition to systemic cross-organ signaling, EV-miRNA communication also shapes local tissue remodeling. Fry *et al* (197) demonstrated that during mechanical overload-induced skeletal muscle hypertrophy, myogenic progenitor cells (MPCs) regulate the stromal microenvironment through exosome-mediated transfer of miR-206. MPC-derived exosomes delivered miR-206 to fibrogenic cells, suppressed its target gene ribosome binding protein 1 (*Rrbp1*), reduced collagen and other extracellular matrix-related transcripts, and thereby limited excessive fibrosis while supporting appropriate muscle remodeling. By contrast, loss of MPCs or disruption of miRNA processing/exosomal miR-206 signaling exacerbated extracellular matrix deposition and impaired remodeling quality. These findings establish a direct mechanistic axis linking mechanical loading, EV-mediated miRNA transfer, recipient-cell gene reprogramming, and tissue adaptation (197).

Table III. Epigenetic effects associated with exercise-induced EVs.

Exercise protocol	EV source/ sample	Epigenetic change (cargo remodeling)	Epigenetic effects	Year	(Refs.)
Single flywheel-based iso-inertial resistance session in trained men	Circulating EVs from blood	Acute exercise increased EV-encapsulated miR-206 and miR-146a	Suggests rapid EV-mediated transfer of regulatory miRNAs during early post-exercise adaptation, potentially coupling inflammation to muscle remodeling	2019	(194)
Acute exercise/fitness-related comparison in young men	Plasma EVs, including $SGCA^+$ muscle-enriched EVs	Muscle-derived EVs were enriched in miR-206; EV miR-133b and miR-181a-5p increased after acute exercise	Supports skeletal muscle as a source of circulating EV-miRNAs that may contribute to muscle remodeling, homeostasis, and inter-organ communication	2015	(68)
Two consecutive bouts of muscle-damaging exercise (plyometrics + downhill running)	Plasma EVs	No major change in EV number or canonical myomiRs; EV miR-31 decreased at 24 h	Indicates selective EV cargo repackaging after muscle-damaging exercise, with miR-31 emerging as a potential regulator of early recovery/remodeling	2018	(195)
Acute uphill vs. downhill running in rats	Plasma, exosomal, and exosome-free fractions	After downhill exercise, exosomal miR-1, miR-133a, miR-133b, miR-206, miR-208a, miR-499 increased during early recovery; uphill exercise produced little exosomal change	Suggests exercise mode-specific EV-miRNA remodeling, with eccentric loading preferentially engaging exosomal miRNA signaling during recovery	2019	(73)
Acute 40-min cycling in sedentary vs. endurance-trained older men; comparison of chronic training status	Plasma exosomes	Baseline exomiR profiles differed by training status; acute exercise-induced distinct exomiR signatures in trained vs. sedentary men	Suggests regular training reshapes EV-mediated epigenetic signaling and may counteract age-related anabolic resistance	2020	(196)
Long-term swim training in rats; trained vs. untrained human volunteers	Circulating plasma exosomes	Long-term exercise enriched exosomal miR-342-5p without changing total exosome abundance at 24 h	Exercise-derived exosomes conveyed sustained cardioprotection, reduced cardiomyocyte apoptosis, and protected against myocardial ischemia/reperfusion injury	2019	(45)
Treadmill exercise in db/db diabetic mice	Serum and heart-associated exosomes ('cardiosomes')	Exercise enhanced exosomal release and increased miR-29b and miR-455	Reduced MMP9 activity, attenuated extracellular matrix remodeling, and potentially limited fibrosis and diabetic cardiac injury	2015	(147)

EVs, extracellular vesicles; miR or miRNA, microRNA; SGCA, α-sarcoglycan; exomiR, exosomal microRNA; MMP9, matrix metalloproteinase 9; db/db, leptin receptor-deficient diabetic mice.

Although much of the available literature remains associative, several recent studies have begun to provide stronger functional support that exercise-responsive EV-miRNA cargoes can regulate recipient-cell gene programs and tissue adaptation (34,198). In particular, some reports now extend beyond descriptive profiling by linking exercise-induced changes in EV-miRNA cargo to downstream target repression and measurable phenotypic effects in recipient tissues.

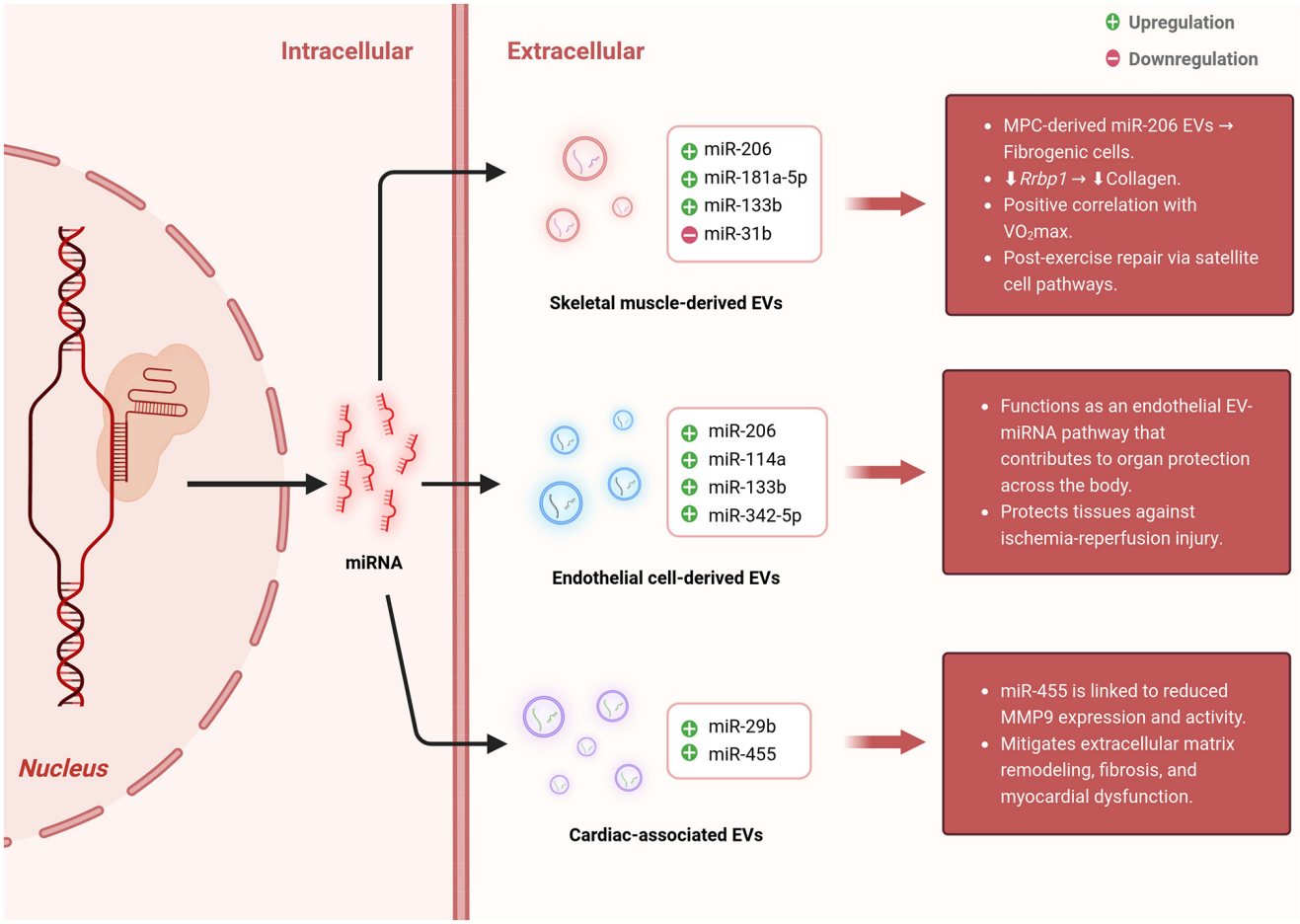

Figure 2. Representative exercise-responsive miRNAs enriched in EVs and their potential biological functions. The schematic summarizes representative miRNAs carried by exercise-responsive EVs from different cellular or tissue-associated sources. Exercise may alter the abundance of EV-associated miRNAs released from skeletal muscle-related cells, endothelial cells, and cardiac-associated compartments. Skeletal muscle-derived EV miRNAs, including miR-206, miR-181a-5p, miR-133b, and miR-31, are implicated in muscle remodeling, satellite cell-related repair, fibrogenic cell regulation, and exercise capacity. Endothelial cell-derived EV miRNAs, such as miR-206, miR-114a, miR-133b, and miR-342-5p, may contribute to vascular and organ-protective responses, including protection against ischemia-reperfusion injury. Cardiac-associated EV miRNAs, including miR-29b and miR-455, have been linked to regulation of extracellular matrix remodeling, fibrosis, and myocardial dysfunction. Green and red symbols indicate reported upregulation and downregulation, respectively. Together, these examples illustrate how exercise-induced EV-miRNA remodeling may connect local cellular responses with systemic tissue protection and adaptive remodeling. EVs, extracellular vesicles; miR, microRNA; MPC, myogenic progenitor cell; Rrbp1, ribosome binding protein 1; MMP9, matrix metalloproteinase 9.

In a diabetic heart model, exercise-induced enrichment of EV-associated miR-455 was linked to reduced MMP9 expression and attenuation of extracellular matrix remodeling and myocardial dysfunction (146). Similarly, exercise-responsive exosomal miR-342-5p has been functionally linked with suppression of apoptosis-related targets and enhanced cardioprotection (45). Among the currently available examples, the MPC-derived exosomal miR-206/Rrbp1 axis provides especially direct support that EV-mediated miRNA transfer can reshape recipient-cell gene expression and local tissue remodeling (197). Nevertheless, direct evidence that specific exercise-responsive EV-miRNA cargoes induce canonical epigenetic remodeling in recipient tissues, rather than broader post-transcriptional or signaling changes, remains limited and warrants further investigation.

Unresolved challenges in EV research. Current studies suggest that exercise-induced EV remodeling may contribute to cross-organ metabolic adaptation, inflammatory regulation, and tissue protection, but the field remains largely at a transitional stage between descriptive observation and mechanistic validation (34,37,118,199). A major limitation is methodological heterogeneity, much of which arises from differences in EV isolation and characterization strategies. Commonly used EV isolation techniques include differential ultracentrifugation, size exclusion chromatography, and immunoaffinity-based isolation, each with distinct strengths and limitations in terms of recovery, purity, and subtype selectivity (200). In general, ultracentrifugation is widely used but may co-isolate contaminants, size exclusion chromatography often improves purity, and immunoaffinity-based approaches provide higher specificity for selected EV populations (201). Terminology remains inconsistent across studies, with EVs, exosomes, microvesicles, and small EVs often used interchangeably, even though isolation procedures alone are usually insufficient to define vesicle subtype with precision (202). As emphasized in the Minimal Information for Studies of Extracellular Vesicles (MISEV)2018 recommendations, no single method is universally optimal, and isolation procedures alone are often insufficient to define EV subtypes

with precision (48). MISEV2018 therefore advocates the use of 'extracellular vesicle' as a generic term when subtype assignment remains uncertain, together with transparent reporting of isolation workflows, complementary characterization methods, inclusion of both positive and negative markers, and careful assessment of co-isolated non-vesicular contaminants. These considerations are particularly important in exercise-EV studies, where methodological variation can substantially affect the apparent abundance, composition, and inferred function of circulating EV preparations (48). In addition, plasma and serum contain lipoproteins, albumin, and protein-RNA complexes that overlap extensively with small EVs in size and physicochemical properties; when sample purity is inadequate, apparent changes in EV number or EV-miRNA cargo may be misinterpreted (203). Another critical source of confounding, particularly in training studies, is sampling time. Because circulating small EV dynamics can be rapid, samples collected too close to the final exercise bout may reflect acute release and clearance rather than true training-induced homeostatic remodeling, thereby obscuring the distinction between acute responses and chronic adaptation (66). At the same time, although numerous studies report exercise-associated changes in circulating miRNA profiles, direct evidence remains limited regarding their precise tissue origins, dominant carrier subtypes, destination organs, and functional uptake (37,65,204). Moving the field forward will therefore require more rigorous experimental design under the MISEV framework. This includes improved EV isolation and characterization using multi-step workflows, more systematic reporting of positive and negative markers as well as contamination indicators, and clearer separation of acute stress responses from chronic training adaptations through appropriate sampling windows (such as ≥24-48 h after the last exercise bout). Recent advances in multi-omics are also helping to refine EV characterization beyond particle counting and bulk marker detection (205). Integrative analyses combining proteomics, lipidomics, and surfaceome profiling can improve discrimination between circulating EVs and non-vesicular contaminants, while providing a more detailed molecular map of EV composition in human plasma (206). For the exercise-EV field, these approaches may be especially useful for resolving vesicle heterogeneity, identifying tissue-informative cargoes, and connecting EV remodeling with downstream metabolic and epigenetic effects. More importantly, tissue-specific tracing, single-particle profiling, and causal intervention studies will be needed to define the contribution of distinct EV subtypes to ncRNA-mediated inter-organ communication and to clarify how these signals intersect with DNA methylation, histone modification, chromatin accessibility, and transcriptional reprogramming (203).

An additional translational limitation is that much of the current mechanistic framework has been established in animal models or cell-based systems, whereas direct human evidence remains comparatively limited. In preclinical studies, exercise-derived EVs have been linked to specific miRNA cargoes, downstream target regulation, and functional effects in recipient tissues. By contrast, most human studies still rely on measurements of circulating EV abundance, surface markers, or cargo associations before and after exercise, without directly establishing tissue origin, target-organ delivery, cellular uptake, or causal contribution to physiological adaptation. As a result, although the available data strongly support the biological plausibility of EV-mediated exercise signaling, the extent to which these mechanisms operate in humans remains incompletely resolved. Bridging this gap will require better integration of mechanistic preclinical studies with rigorously designed human investigations that incorporate refined EV characterization, longitudinal sampling, and functional validation.

Overall, as methodological standardization, refined EV subtyping, and integrative multi-omics approaches continue to advance, research on the exercise-EV-miRNA-epigenetic axis is likely to move from predominantly descriptive association toward more reproducible and causally interpretable mechanistic investigation. Such progress will not only deepen our understanding of how exercise promotes systemic health and metabolic adaptation, but may also support the development of biomarkers of exercise responsiveness, more precise exercise prescriptions, and future exercise-mimetic strategies.

6. Conclusions

EVs have emerged as key mediators of the systemic benefits of exercise. Far from being passive by-products of cellular stress, they act as dynamic carriers of bioactive cargo, including proteins, metabolites, and regulatory ncRNAs, that transmit exercise-induced signals to recipient cells and reshape downstream signaling and gene expression. Both acute and chronic exercise induce context-dependent remodeling of EV abundance, origin, and cargo, influenced by factors such as exercise modality, intensity, timing, training status, and host characteristics. Among the various cargoes, miRNAs play a particularly pivotal role as mobile epigenetic regulators that link exercise to sustained changes in metabolism, inflammation, tissue repair, and organ protection (Fig. 2). Current evidence supports the exercise-EV-epigenetic axis as a meaningful framework for understanding long-term physiological adaptation. However, progress in the field is still constrained by methodological heterogeneity, inconsistent terminology, and limited mechanistic insight into EV biogenesis, targeting, and functional uptake. Addressing these challenges through rigorous standardization, refined EV characterization, and *in vivo* causal studies will be essential. A clearer understanding of exercise-derived EVs may not only deepen our mechanistic understanding of exercise adaptation, but also advance the development of biomarkers, precision exercise strategies, and EV-based therapeutic approaches. This overall framing is consistent with the synthesis in the present review, in which exercise remodels EV abundance, subtype distribution, and cargo, with miRNAs emerging as a functionally important component, while the field remains limited by heterogeneity and incomplete mechanistic validation.

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Authors' contributions

XZ and BZ contributed to the study conception and design, data collection, figure drawing, and manuscript drafting. Both authors read and approved the final manuscript. Data authentication is not applicable.

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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