



Mechanically remodeled extracellular vesicles: drivers of disease or therapeutic opportunities?

Aoxue Wang^{1,#}, Hangrui Xu^{1,#}, Hang Liu², Biao Yan³, Ningli Wang⁴, Runlang Zhu¹, Anhuai Yang¹, Liang Hu^{1,2} , Xuan Xiao^{1,2}

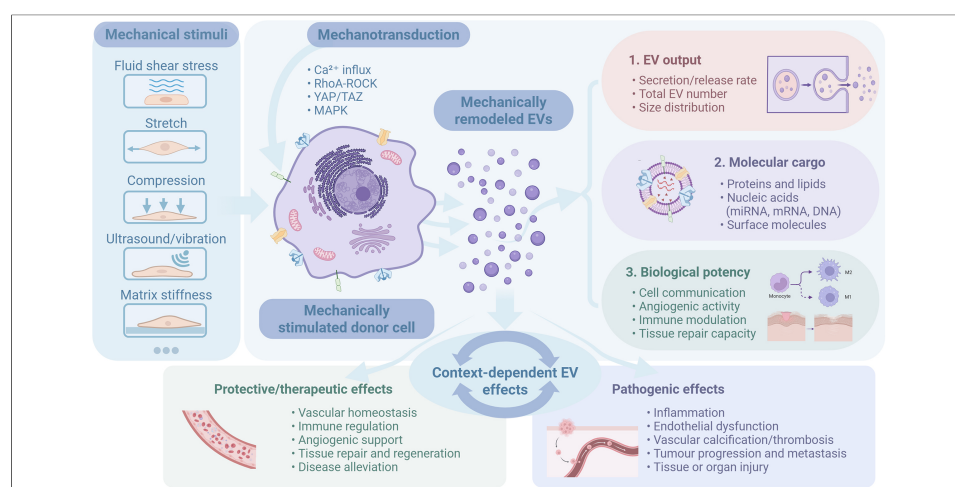
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Abstract

Mechanical signals contribute to tissue homeostasis and disease progression by regulating cell behavior and intercellular communication. Extracellular vesicles (EVs) can relay donor-cell responses to mechanical stimuli to recipient cells, linking the mechanical microenvironment to physiological and pathological changes. Drawing on 98 studies published between January 2015 and February 2026, this review examines the connections between mechanical stimulation, EV remodeling and biological outcomes. We outline the mechanisms linking cellular mechanosensing and mechanotransduction to EV biogenesis, release and molecular remodeling, alongside changes in EV abundance, size, cargo, and function. We then discuss how these changes shape EV activity under conditions of physiological homeostasis, adaptive stress and pathological loading. Mechanically remodeled EVs can support homeostasis and tissue repair or promote disease progression, depending on the stimulus characteristics and the environments of donor and recipient

¹Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China.

²Department of Clinical Laboratory, Institution of Translational Medicine, Renmin Hospital of Wuhan University, Wuhan 430000, Hubei, China.

³Department of Ophthalmology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200080, China.

⁴Department of Ophthalmology, Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China.

These authors contributed equally to this work.

Correspondence to: Prof. Liang Hu, Department of Clinical Laboratory, Institution of Translational Medicine, Renmin Hospital of Wuhan University, Wuhan 430000, Hubei, China. E-mail: lianghu22@whu.edu.cn; Prof. Xuan Xiao, Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan 430060, Hubei, China. E-mail: xiaoxuan1111@whu.edu.cn

cells. Beyond their local and distant effects, EVs may also contribute to feedback regulation of mechanical responses. Such feedback may involve direct effects on donor cells or changes in the local microenvironment mediated by neighboring cells. These proposed mechanisms require further direct experimental support. By connecting mechanical inputs with EV remodeling and function, this Review offers a framework for understanding intercellular communication within the mechanical microenvironment. It also considers implications for optimizing therapeutic EV production and exploring interventions in disease.

INTRODUCTION

Mechanobiology centers on two fundamental questions: how cells sense mechanical forces and how these forces drive functional remodeling in disease^[1-3]. This has fueled the emergence of “mechanomedicine”, a discipline that treats the mechanical properties of tissues and cells as quantifiable biological variables. In this framework, mechanical signals and their regulatory pathways are viewed as pivotal targets for diagnosis, dynamic monitoring, and therapeutic intervention^[4].

These concepts are deeply grounded in biomechanical theory. As a bridge between the physical microenvironment and cellular behavior, biomechanics is indispensable to tissue engineering, regenerative medicine, and mechanistic disease research^[5]. *In vivo*, cells are subjected to diverse mechanical stimuli, including fluid shear stress, tension, compression, hydrostatic pressure, and extracellular matrix stiffness, all of which maintain tissue homeostasis or drive pathogenesis by modulating cellular mechanosensation^[6].

Within this regulatory framework, extracellular vesicles (EVs), as pivotal mediators of intercellular transport and signaling^[7,8], serve as essential messengers bridging mechanical stimuli with downstream biological effects^[9]. Extensive evidence reveals that mechanical stimulation does more than directly alter cellular phenotypes^[10]; it orchestrates the biogenesis, membrane morphology, and cargo profiles of EVs, thereby refining their impact on recipient cells^[11]. Consequently, mechanically driven EVs play indispensable roles in tissue remodeling^[12-14], inflammatory responses^[15,16], and regenerative repair^[17,18].

This review examines how mechanical forces regulate cells and their secreted EVs. We systematically summarize the past decade's progress, emphasizing how cells respond to the mechanical microenvironment and how these responses dictate EV biogenesis and functional remodeling. Furthermore, we delineate the distinct biological characteristics of EVs induced by various mechanical stimuli. On this basis, we evaluate the potential of mechanically modulated EVs in disease pathogenesis and preclinical therapeutics, aiming to provide a robust theoretical foundation for basic research and translational applications.

EXTRACELLULAR VESICLE BIOLOGY: DEFINITION, BIOGENESIS AND SECRETION

EVs are cell-released particles that are enclosed by a lipid bilayer and cannot replicate independently^[19]. They are widely distributed in biological fluids and tissues and can carry donor-cell-derived proteins, lipids, nucleic acids, and metabolites^[19]. By interacting with recipient cells or transferring molecular contents to them, EVs participate in intercellular communication and modulate physiological and pathological processes^[7,20].

EV biogenesis and secretion involve coordinated steps of cargo selection, membrane remodeling, vesicle formation, intracellular transport, membrane tethering, and extracellular release^[7,21]. In the endosomal pathway, specific membrane proteins and cytosolic cargo are sorted into endosomal membrane microdomains^[22,23]. Inward budding of the endosomal membrane then generates intraluminal vesicles (ILVs)^[23]. ILV formation may involve cargo capture and membrane scission mediated by the endosomal sorting complexes required for transport (ESCRT)^[22,24]. Alternatively, context-dependent

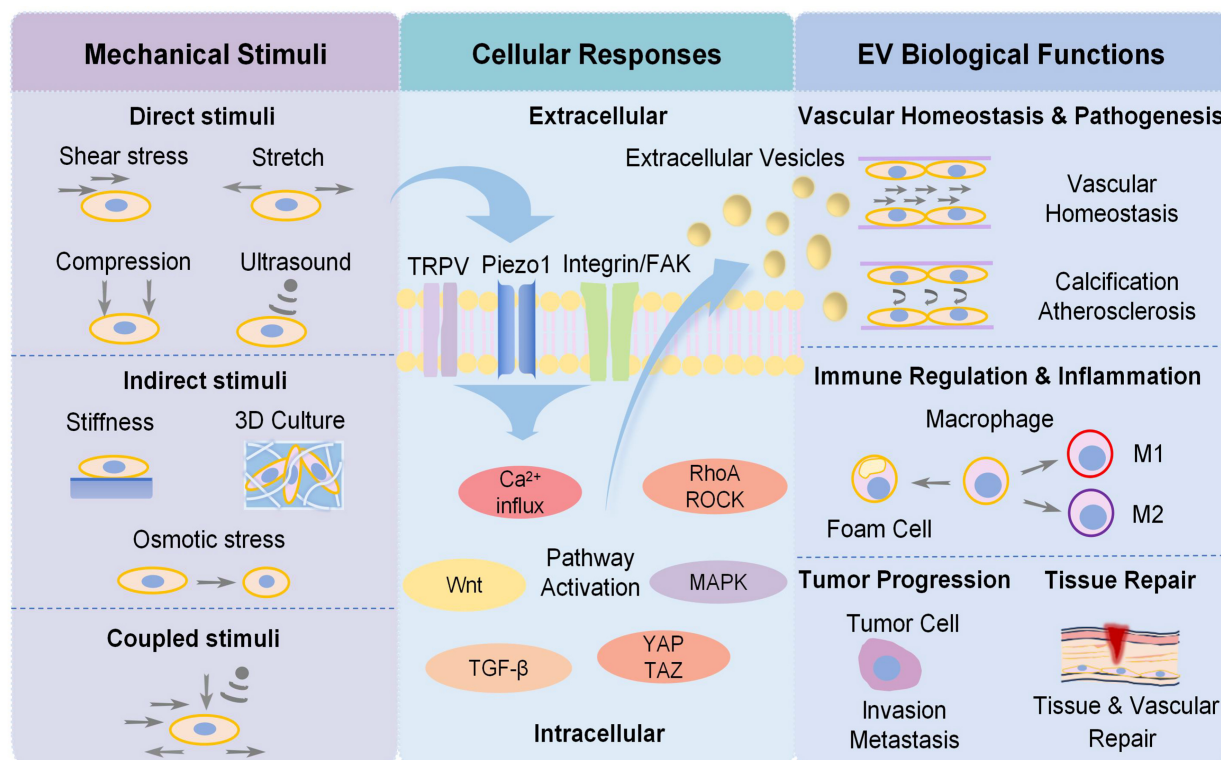


Figure 1. Mechanical regulation of EV biogenesis and function: a mechanobiological perspective. 3D: Three-dimensional; Ca^{2+} : calcium ion; EV: extracellular vesicle; FAK: focal adhesion kinase; MAPK: mitogen-activated protein kinase; M1: classically activated macrophages; M2: alternatively activated macrophages; Piezo1: Piezo-type mechanosensitive ion channel component 1; RhoA: Ras homolog family member A; ROCK: Rho-associated coiled-coil-containing protein kinase; TAZ: transcriptional co-activator with PDZ-binding motif; $\text{TGF-}\beta$: transforming growth factor beta; TRPV: transient receptor potential vanilloid; Wnt: wingless-related integration site; YAP: Yes-associated protein.

ESCRT-independent mechanisms can be driven by lipids such as ceramide or by tetraspanins^[23-25]. Mature multivesicular bodies (MVBs) can be directed towards lysosomal degradation or transported along the cytoskeleton to the plasma membrane. The secretory route involves Rab GTPase-dependent positioning and tethering, followed by soluble N-ethylmaleimide-sensitive factor attachment protein receptor-mediated fusion of MVBs with the plasma membrane^[26-28]. ILVs released through this fusion should be termed exosomes only when their endosomal origin has been experimentally established^[19]. By contrast, plasma membrane-derived EVs, often termed microvesicles or ectosomes, form through outward budding of the plasma membrane and are released by membrane scission. This process may involve lipid redistribution, cortical actomyosin remodeling, ADP-ribosylation factor 6 (ARF6) signaling, and arrestin domain-containing protein 1 (ARRDC1)-mediated recruitment of tumor susceptibility gene 101 and vacuolar protein sorting-associated protein 4^[19,29,30].

MECHANICAL STIMULATION AND MECHANOSENSITIVE REGULATION OF EV BIOGENESIS AND RELEASE

Operational classification of mechanical stimulation and evidence framework

In vivo, cells typically encounter several mechanical cues simultaneously, including fluid shear, stretch, compression, hydrostatic pressure, and matrix mechanical properties. *In vitro* studies isolate specific mechanical variables using single-factor models or reproduce complex mechanical environments through three-dimensional (3D) culture and bioreactors. To examine how these stimuli regulate cells and their secreted EVs, we classified them by the primary route through which mechanical information reaches cells. This operational classification comprises direct, indirect or environment-mediated, and coupled stimuli [Figure 1].

Direct forces refer to explicit and controllable physical loads applied directly to cells or tissues by external sources, including fluid shear stress^[14-16,31-49], ultrasound^[18,50-69] or acoustic waves^[70], stretch^[12,13,36,71-82] and compression^[11,83-87]. These stimuli engage the cell membrane, cytoskeleton, and mechanosensory structures on a short time scale, rapidly triggering biological responses.

Indirect forces arise as cells actively or passively adapt to environmental changes induced by a single experimental intervention. Their mechanical effects emerge from cell-environment interactions and therefore depend more strongly on cell type, state, geometry, and exposure duration. Examples include confinement and matrix architecture associated with 3D culture^[88-92], matrix stiffness^[93-101] and osmotic pressure^[102-106]. Through cell-matrix interactions, 3D culture and matrix stiffness alter cell geometry, adhesion and cytoskeletal tension. Osmotic stimuli act through volume-mediated mechanisms, whereby transmembrane water flux changes cell or organelle volume. These volume changes, in turn, affect membrane tension, curvature and the capacity for membrane remodeling.

Coupled stimulation describes the exposure of cells or tissues to two or more mechanical factors simultaneously^[17,82,107-120], reflecting the synergistic or superimposed effects of complex signaling. This classification describes how stimuli are applied and the extent to which their effects can be resolved experimentally. It does not imply that the three categories correspond to distinct mechanotransduction or EV biogenesis pathways.

On this basis, to evaluate the distribution of different types of mechanical stimuli in EV research, we systematically searched peer-reviewed original research articles published from January 2015 to February 2026 (primarily in PubMed and supplemented by Google Scholar). A combined keyword strategy was adopted: EV-related terms (“extracellular vesicles”, “exosomes”, or “vesicles”) were combined with mechanical stimulation-related terms (“mechanical stimulation”, “shear stress”, “ultrasound”, “three-dimensional culture”, “substrate stiffness”, “compression”, “stretch”, “osmotic pressure”, or “bioreactor”) using Boolean AND operators. Eligibility and data extraction were determined at the level of individual experimental comparisons or stimulus instances rather than entire publications. A comparison within a multi-arm study was eligible if mechanical stimulation was the only intervention differing between the experimental group and its matched control. This applied even when the same study included chemical-only or combined mechanical-chemical treatment groups. When a study investigated multiple eligible mechanical modalities, each modality was counted as a distinct stimulus instance. Coupled mechanical stimulation was defined as the simultaneous application of two or more mechanical stimuli, excluding combinations of mechanical and non-mechanical interventions. Studies were excluded when any of the following conditions were met: (1) mechanical stimulation was applied only alongside chemical or biological interventions, with no separately evaluable mechanical-only comparison; (2) mechanical stimulation was not applied to EV-producing donor cells or tissues; or (3) no EV-specific outcomes were assessed, including EV biogenesis, release or abundance, size, molecular composition, or biological function.

The final dataset comprised 98 eligible studies, yielding 101 distinct mechanical stimulation cases for quantitative analysis. Direct stimulation accounted for the largest proportion of cases (65.35%, 66/101), followed by indirect stimulation (18.81%, 19/101) and coupled stimulation (15.84%, 16/101). Ultrasound and fluid shear stress were the most frequently studied modalities [Figure 2A]. Subsequent analyses of the biological characteristics and functional differences of EVs under distinct mechanical conditions were conducted using this classification framework.

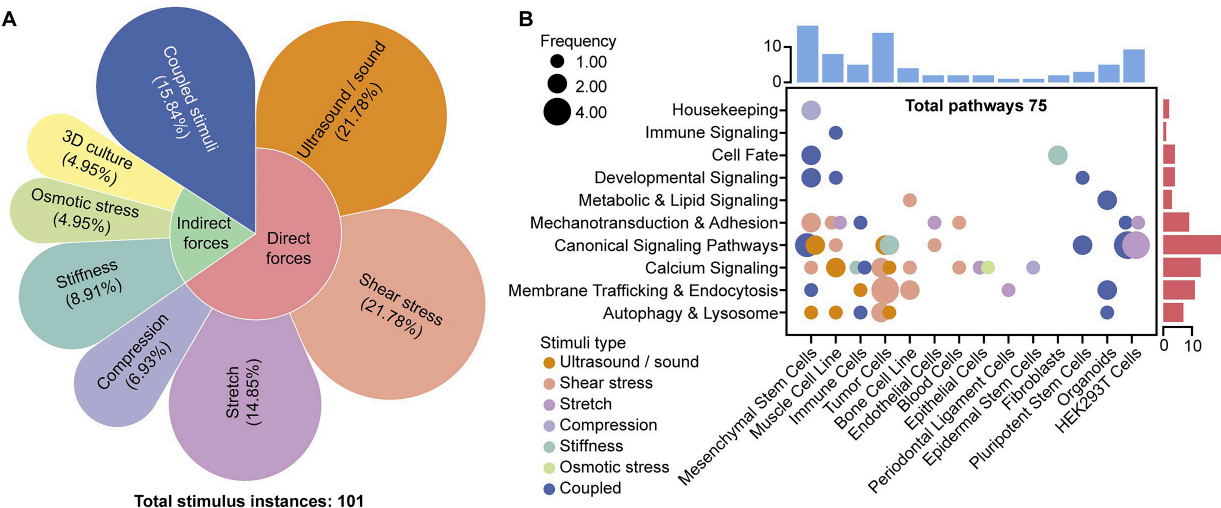


Figure 2. Literature analysis of mechanical stimulation categories and associated signaling pathways. (A) Distribution of different mechanical stimulation types across the included studies; (B) Frequency of signaling pathways and cell types implicated in mechanotransduction. Pathways were annotated using the KEGG database and categorized by their biological functions. 3D: Three-dimensional; HEK293T: human embryonic kidney 293T; KEGG: Kyoto Encyclopedia of Genes and Genomes.

Cellular responses to mechanical stimulation

Cells sense extracellular mechanical signals through diverse mechanisms and mount adaptive responses to biomechanical microenvironmental alterations. This process is not a simple linear reaction but features highly dynamic and nonlinear regulatory characteristics^[103]. Such time dependence unfolds in sequential phases: an early rapid response phase dominated by mechanical signal sensing and transduction; an intermediate phase involving cytoskeletal remodeling and homeostatic adjustment to restore structural and functional stability; and a late persistent adaptation phase characterized by metabolic reprogramming and phenotypic regulation^[50,121,122]. Changes in membrane tension can activate mechanosensitive ion channels such as Piezo, producing rapid ion fluxes-particularly Ca^{2+} influx-and initiating downstream signaling^[1,123]. In parallel, forces transmitted through integrins and focal adhesions promote integrin clustering, thereby activating focal adhesion kinase (FAK)/Src, Rho-family GTPases and actomyosin contractility^[124,125]. Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are important nuclear effectors of mechanical signaling, and their nuclear accumulation is regulated by extracellular-matrix stiffness, cell geometry and cytoskeletal tension^[126]. These signals can also interact with context-dependent biochemical pathways, including mitogen-activated protein kinase (MAPK), wntless-related integration site (Wnt)/ β -catenin and transforming growth factor beta (TGF- β)/Smad signaling^[6,127-130]. Consequently, the cellular response varies with stimulus magnitude, loading rate, frequency and duration, as well as cell type and pre-existing state.

To systematically dissect the characteristics of mechanical stimulation-induced signaling pathways and their associations with stimulus types and cell types, we curated the signaling pathways reported in the literature and classified them according to the Kyoto Encyclopedia of Genes and Genomes (KEGG) database [Figure 2B]. The results revealed that besides the broad activation of canonical pathways (e.g., MAPK and Wnt/ β -catenin), the calcium signaling pathway was reported across nearly all types of mechanical stimulation, with the highest prevalence under direct stimulation. These findings further confirm that calcium signaling represents the most direct and universal signaling module in cellular mechanotransduction. In addition, pathways related to membrane trafficking and endocytosis also showed high activation frequencies, suggesting that EV biogenesis is a primary cellular response to mechanical stimulation.

Among the included studies, mesenchymal stem cells (MSCs) were the most commonly investigated cell type. MSCs activated multiple signaling pathways under mechanical stimulation [Figure 2B], demonstrating strong mechanosensitivity and signal integration capacity. Previous studies have largely focused on the therapeutic potential of mechanoresponsive EVs, with MSCs^[131,132] being one of the most frequently used source cells—a trend consistent with our statistical results. Tumor cells and the human embryonic kidney 293T (HEK293T) tool cell line followed in frequency. The former underscores the critical link between the mechanical microenvironment and tumor progression, while the latter, similar to MSCs, mainly serves as a producer of therapeutic EVs.

Mechanistic links between mechanosensitive signaling and EV biogenesis and release

Mechanical signals may influence several stages of EV biogenesis and release. Mechanosensitive ion channels, integrin-mediated adhesions and the cytoskeleton can link mechanical inputs to Ca^{2+} signaling, membrane remodeling and vesicle trafficking^[132,133]. In MLO-Y4 osteocyte-like cells, fluid shear induces Ca^{2+} oscillations accompanied by actomyosin contractions and increases EV release^[14]. Pharmacological inhibition of Ca^{2+} signaling with neomycin attenuates the flow-induced increase in EV release^[14]. In a separate plasma membrane injury model, Ca^{2+} influx can promote the recruitment of annexin A6 (ANXA6) to cluster of differentiation 63 (CD63)-positive MVBs. ANXA6 contributes to MVB transport to the plasma membrane and subsequent tethering and fusion, providing a mechanistic basis for Ca^{2+} -dependent EV release^[134]. Osmotic pressure can influence intraluminal vesicle formation through an endosomal tension-ESCRT-III pathway^[135]. Matrix stiffening can promote MVB transport towards the cell periphery and increase EV release through the FAK-Akt-Rab18-Rab8 axis^[95]. For plasma membrane-derived EVs, actomyosin contraction regulated by ARF6 and the Ras homolog family member A (RhoA)-Rho-associated coiled-coil-containing protein kinase (ROCK) pathway can promote scission at the neck of budding vesicles and their subsequent release^[29,136]. In dynamic 3D cultures or bioreactor systems, cell aggregation, matrix contact, mass transfer and shear typically change together^[113,114]. Current evidence therefore primarily supports the combined influence of multiple factors, but cannot yet distinguish additive, synergistic or antagonistic effects. These findings derive from different experimental models: some studies directly link specific mechanical stimuli to EV formation or release, whereas others identify membrane remodeling and trafficking mechanisms that may be engaged by mechanical signaling. Together, they do not yet establish a complete causal chain applicable across all stimulation conditions.

Mechanical remodeling of EV output and phenotype

Since previous studies have consistently shown that mechanical stimulation activates pathways associated with vesicle biogenesis, we examined reported changes in EV output. Given the heterogeneity in cell types and quantification methods, we used fold changes relative to matched controls as the primary measure rather than comparing absolute values [Figure 3]. Comparison-level details of EV sources, isolation and quantification methods, normalization approaches, and other available experimental information are provided in [Supplementary Table 1](#). Ultracentrifugation was the most frequently used isolation method, but no clear association emerged between isolation strategy and the magnitude of relative changes in EV output [Figure 3A]. Increased EV output was reported in 88.14% of the included stimulation instances, with coupled and acoustic stimulation most frequently represented [Figure 3B]. Nevertheless, heterogeneity in cell types, quantification methods, and assessment criteria limits cross-study comparisons and does not support a general conclusion that mechanical stimulation significantly increases EV output^[137].

When grouped by cell type, the data showed an overall trend towards increased EV output across cell categories [Figure 3C]. Stem/progenitor cells and differentiated/functional cells were the two most extensively studied categories, with larger relative changes observed in the former. This difference may reflect cellular mechanosensitivity, but could also arise from differences in culture conditions, proliferative state,

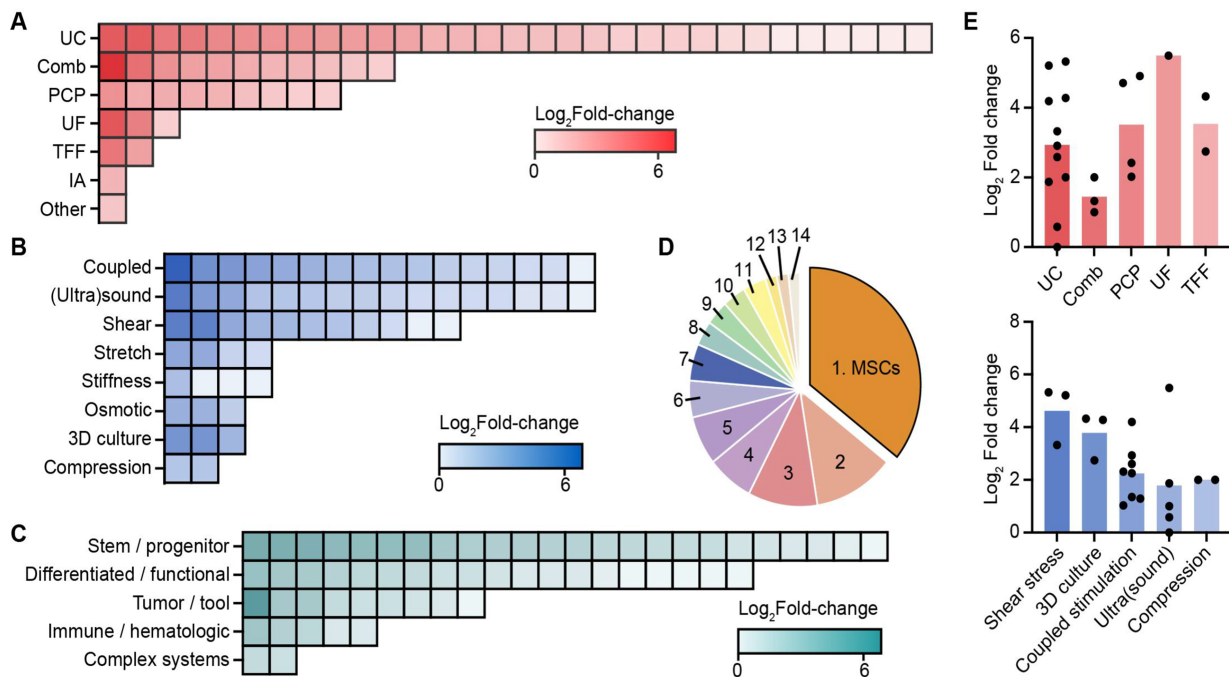


Figure 3. Exploratory summary of reported changes in EV output following mechanical stimulation. (A) Fold changes grouped by EV isolation method; (B) Fold changes grouped by mechanical stimulation type; (C) Fold changes grouped by donor-cell type; (D) Distribution of donor-cell types investigated. The cell types are as follows: 1. mesenchymal stem cells; 2. muscle cell lines; 3. tumor cells; 4. immune cells; 5. endothelial cells; 6. neuronal and glial cells; 7. HEK293T cells; 8. preadipocytes; 9. fibroblasts; 10. bone cell lines; 11. organoids; 12. blood cells; 13. epithelial cells; and 14. pluripotent stem cells; (E) Stratified analysis of reported changes in EV output for the MSC studies represented in panel D, grouped by isolation method (top) and stimulation modality (bottom). Note: This figure descriptively summarizes heterogeneous study-specific measurements of EV output. Fold change was calculated as the ratio of the reported output in the mechanically stimulated group to that in the matched control group. Studies without clearly reported changes in EV output were excluded. EV output includes EV concentration, total recovered EV number and cell-normalized EV productivity, as defined in each original study. Comparison-level details of EV sources, isolation and quantification methods, normalization approaches and other available experimental information are provided in [Supplementary Table 1](#). Within-study ratios do not eliminate differences in quantification methods, normalization, isolation recovery or sample purity. Accordingly, comparisons across groups should be interpreted as exploratory patterns in the available literature. Values are displayed as $\log_2(\text{stimulated}/\text{control})$, with the transformation used solely for visualization. EV: Extracellular vesicle; 3D: three-dimensional; Comb: combined separation strategies; HEK293T: human embryonic kidney 293T; IA: immunoadsorption; MSCs: mesenchymal stem cells; PCP: polymer co-precipitation; TFF: tangential flow filtration; UC: ultracentrifugation; UF: ultrafiltration.

and the number of studies available for each category. We separately summarized studies using MSCs to describe reported EV output changes within a more comparable donor-cell category, while recognizing differences in tissue origin and culture conditions [Figure 3D and E]. No consistent pattern emerged across isolation methods. In addition, EV productivity responses to bioreactor culture varied among MSCs from different tissue sources. The mean bioreactor-to-static fold changes in cell-normalized EV productivity (particles/cell) were 1.4 ± 0.3 , 3.7 ± 1.0 and 3.9 ± 1.4 for bone marrow-, adipose tissue- and umbilical cord matrix-derived MSCs, respectively^[118]. These findings suggest that EV responses to mechanical stimulation may depend strongly on cell type. Given the limited sample size and the factors discussed above, these results should be interpreted as preliminary, descriptive trends rather than a definitive ranking of stimulus efficacy.

These results must also be interpreted in light of the limitations of EV quantification. Reported EV output reflects not only biological release but also medium volume, collection duration, viable cell number, storage conditions and pre-analytical handling^[19,118,138,139]. Ultracentrifugation, precipitation, size-exclusion chromatography and tangential flow filtration differ in recovery, separation specificity and the extent of non-vesicular co-isolation^[140-142]. Even when expressed as fold changes relative to controls, comparisons may remain biased by differences in baseline recovery, sample purity and detection sensitivity across studies^[19,143].

Figure 3 should therefore be interpreted as an exploratory analysis of the available evidence, not a cross-study ranking of mechanical stimuli by their ability to promote EV release. Future studies should use standardized, matched culture, isolation and detection protocols within comparable study designs. These protocols should incorporate orthogonal EV characterization, recovery controls, normalization to viable cell number and collection duration, and functional potency assays. Such measures would help define the methodological limits of EV quantity comparisons and improve cross-study comparability and reliability.

Most literature demonstrates that mechanical stimulation does not significantly alter the average diameter of EVs^[11,13,43,44,92,109], but it can reshape their size distribution under specific conditions^[86,98,102]. Temporally, short-term stimulation exerts minimal effects on overall vesicle dimensions, whereas prolonged or continuous stimulation modifies the homogeneity and subpopulation profiles, indicating time-dependent regulation^[116]. Distinct types of mechanical stimulation also exert selective effects. For example, low-intensity pulsed ultrasound primarily modulates the size distribution of EVs derived from stem cells of the apical papilla, manifested as an increased proportion of large vesicles^[62]. By contrast, mechanical compression or lateral impact elevates the fraction of small vesicles while reducing the relative abundance of large ones^[87]. Furthermore, substrate stiffness mediates a nonlinear, biphasic regulation of EV size: vesicle diameter tends to increase below a stiffness threshold (approximately 20 kPa), but decreases with further increases in stiffness, suggesting a threshold-dependent mechanism^[99].

In addition to regulating EV quantity and size characteristics, mechanical stimulation reshapes the cargo composition, including proteins^[96,99], nucleic acids^[77,114], and lipids^[107]. The literature suggests that this regulation is not a simple global shift but rather selective cargo loading and functional reprogramming. For instance, low-intensity pulsed ultrasound increased miR-328-5p and miR-487b-3p in EVs; recipient macrophages treated with these EVs showed increased the anti-inflammatory factor interleukin-10 (IL-10) expression and reduced inflammatory signaling^[61]. Oscillatory strain or fluid shear stress increases the expression of molecules related to stemness or immune escape [e.g., programmed death-ligand 1 (PD-L1)^[80], miR-21^[33]], which in turn modulates cell proliferation, inflammatory responses, and tumor microenvironment regulation. MSC-EVs induced by normal pressure promote corneal tissue repair, partly due to the selective loading of bioactive molecules with anti-inflammatory and pro-regenerative functions^[11]. Furthermore, 3D or dynamic culture systems typically produce EV subpopulations with more complex compositions and higher activity in cell adhesion, migration, cytoskeletal remodeling, and multiple pro-survival signaling pathways^[92]. This suggests that a complex mechanical microenvironment more faithfully mimics the *in vivo* physiological state and may drive EV functions toward a more biologically relevant phenotype.

Taken together, the evidence on EV quantity, size, and cargo suggests that mechanical stimulation should not be expected to alter EV abundance, composition, and function in parallel^[26,132,144,145]. These outputs are regulated at different stages, including vesicle formation, cargo sorting, release, and recipient-cell responses. A study by Yang *et al.* illustrates this dissociation among outputs^[146]. Bone marrow-derived mesenchymal stem cells (BMSCs) were cultured on collagen matrices with similar elastic moduli but different stress-relaxation properties. EV preparations from viscoelastic matrices showed lower particle yields, larger particle sizes, and higher protein content per particle. Yet these preparations had greater *in vitro* activity and improved diabetic wound repair^[146]. Thus, unchanged EV yield does not exclude substantial molecular remodeling, and increased particle counts alone do not establish enhanced regulated EV secretion. Cell injury and co-isolated non-vesicular particles can also increase the measured signal. Direct links between these stages and outputs have been demonstrated only in selected models. The remaining links should be treated as provisional and tested through time-resolved sampling and pathway perturbation^[19,144].

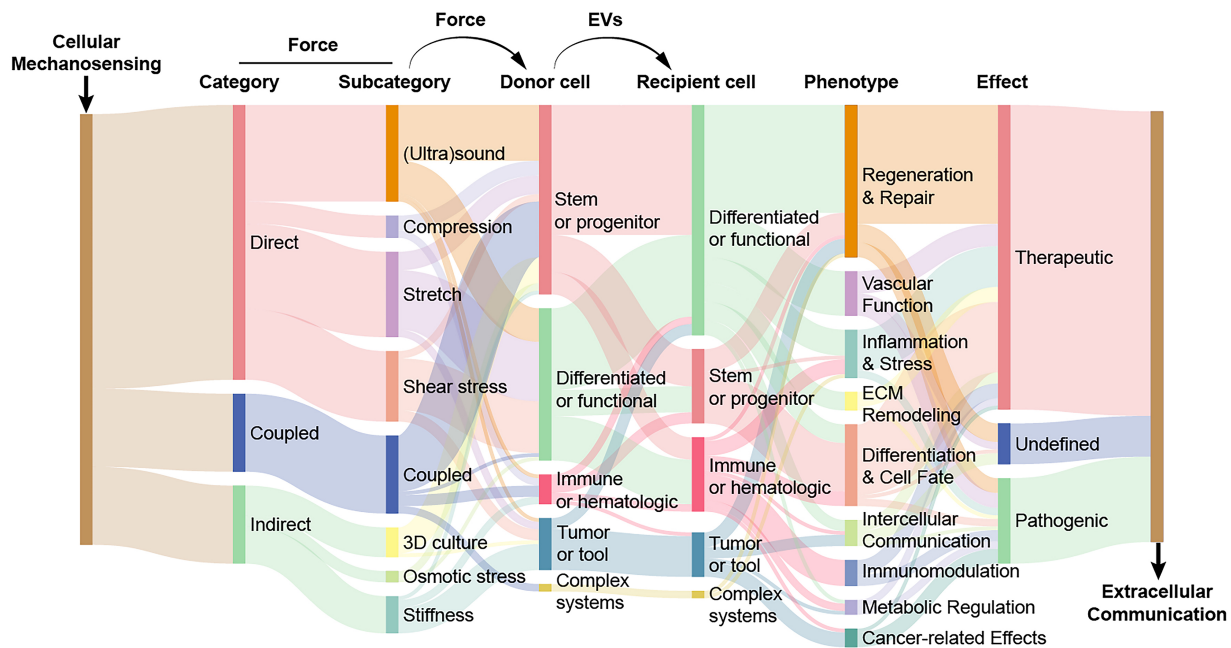


Figure 4. Sankey diagram of multilevel associations from mechanical stimulation to functional outcomes. 3D: Three-dimensional; ECM: extracellular matrix; EVs: extracellular vesicles.

CONTEXT-DEPENDENT DUAL EFFECTS OF MECHANICALLY REMODELED EVs

Changes in EV yield and molecular composition, as discussed in Section “Mechanical remodeling of EV output and phenotype”, do not necessarily predict their functional effects in recipient cells and tissues. We therefore examine how mechanically remodeled EVs contribute to homeostasis, repair, adaptation and disease progression across different biological contexts. The Sankey diagram in [Figure 4](#) integrates reported associations among mechanical stimuli, donor-cell responses, EV remodeling and functional outcomes in recipient cells and tissues. By mapping reported EV transfer routes and their associated biological effects, we assess how mechanically remodeled EVs support tissue protection or contribute to disease. This synthesis also informs our discussion of their potential therapeutic applications [[Table 1](#)].

Homeostatic and reparative effects under physiological or moderate mechanical cues

Under physiological or moderate mechanical stimulation, EVs can contribute to vascular homeostasis, immune balance, and tissue repair. Several studies provide evidence for these effects in specific experimental settings. Atheroprotective shear stress can promote the release of miR-143/145-enriched EVs from endothelial cells through Krüppel-like factor 2 (KLF2). These EVs transfer the miRNAs to vascular smooth muscle cells and regulate gene expression in recipient cells. KLF2-induced endothelial EVs can also reduce atherosclerotic lesions in apolipoprotein E (ApoE)-deficient mice^[147]. EVs from endothelial cells exposed to atheroprotective laminar flow can deliver miR-34c-5p to macrophages and promote macrophage polarization towards the alternatively activated macrophage (M2) phenotype, thereby attenuating inflammation and atherosclerosis-associated responses^[16].

Other mechanical interventions can likewise generate EVs with protective or reparative activity. EVs from endothelial cells exposed to low-intensity pulsed ultrasound can promote the differentiation of cluster of differentiation 4-positive (CD4+) T cells into regulatory T cells (Tregs) and suppress T helper 17 (Th17) cell polarization. These effects can ameliorate inflammatory dilated cardiomyopathy, with miR-99a implicated in the immunomodulatory response^[63]. EVs from periodontal ligament cells subjected to cyclic stretch can also suppress macrophage nuclear factor kappa B (NF- κ B) signaling and interleukin-1 beta (IL-1 β) production,

Table 1. Mechanical-state-dependent remodeling of extracellular-vesicle functions

Stimulation mode	Mechanical state	EV source (donor cells)	Recipient cells/tissues	EV-mediated effects	Pathological/Physiological context	Ref.
Shear stress	Laminar shear stress	Endothelial cells	Macrophages	M1-to-M2 repolarization; reduced plaque inflammation	Atherosclerosis; therapeutic model	[16]
Shear stress	Fluid-flow shear stress	C2C12 myoblasts	Osteoclast precursors	Reduced osteoclast formation vs. static-control EVs	Muscle-bone crosstalk	[32]
Shear stress	Fluid-flow shear stress	M2 macrophages	BMSCs	Enhanced osteogenic differentiation	Fracture healing	[38]
Shear stress	Oscillatory shear stress	Endothelial cells	Endothelial and vascular cells	Associated with impaired LSS signaling, inflammation and vascular dysfunction	Atherosclerosis; vascular remodeling	[46]
Shear stress	Oscillatory shear stress	Endothelial progenitor cells	EPCs	Enhanced EndoMT, inhibited angiogenesis	Pathological vascular remodeling	[45]
Shear stress	Laminar shear stress	Endothelial cells	Endothelial cells	Reduced inflammatory gene expression;	Vascular homeostasis	[43]
Shear stress	Oscillatory shear stress	Endothelial cells	Endothelial cells	Enhanced activation, apoptosis, migration, tube formation, and monocyte adhesion	Vascular dysfunction	[43]
Shear stress	Disturbed flow	Endothelial cells	Monocytes/macrophages	Increased monocyte accumulation, transmigration and M1 polarization	Atherosclerosis	[15]
Shear stress	High-intensity fluid shear stress	Mouse bone-marrow-derived hematopoietic progenitor cells	Osteoclast precursors	Enhanced osteoclast formation	Bone remodeling; bone resorption	[41]
Shear stress	Low-intensity fluid shear stress	Mouse bone-marrow-derived hematopoietic progenitor cells	Osteoclast precursors	Reduced osteoclast formation	Bone remodeling; preservation of bone mass	[41]
Shear stress	High shear stress	Endothelial cells	Endothelial cells	Reduced ROS vs. untreated controls	Atheroprotective vascular context	[40]
Shear stress	Low shear stress	Endothelial cells	Endothelial cells	Increased ROS	Atheroprone vascular context	[40]
Stretch	Cyclic stretch	Periodontal ligament cells	Macrophages	Enhanced M1 polarization and periodontal inflammation	Force-related periodontal inflammation	[73]
Stretch	Cyclic stretch	Periodontal ligament cells	Macrophages	Reduced IL-1 β production and NF- κ B activation	Periodontal immune homeostasis	[72]
Stretch	Tensile stress	Bone-marrow endothelial cells	BMECs and BMSCs	Type H specification; angiogenesis-osteogenesis coupling; bone repair	Segmental bone regeneration	[75]
Stretch	Cyclic stretch	BMSCs	Bone-marrow macrophages/osteoclast precursors	Reduced osteoclastogenesis and unloading-induced bone loss	Bone remodeling; osteoporosis model	[12]
Stretch	Mechanical strain	C2C12 myoblasts	BMSCs	Enhanced proliferation and osteogenesis; reduced glucocorticoid-induced bone loss	Glucocorticoid-induced osteoporosis	[76]
Stretch	Higher-magnitude cyclic stretch	ADSCs	BMSCs and HUVECs	Weaker or inhibitory effects on osteogenesis and angiogenesis vs. 6%-stretch EVs	Diabetic fracture nonunion	[74]
Stretch	Lower-magnitude cyclic stretch	ADSCs	BMSCs and HUVECs	Enhanced osteogenesis, angiogenesis and fracture repair	Diabetic fracture nonunion	[74]
Matrix mechanics	Stiff matrix	HCC cells (including Hepa1-6)	Lung fibroblasts and endothelial cells	Glucose enrichment; angiogenesis; vascular permeability; pre-metastatic niche formation and metastasis	Hepatocellular carcinoma metastasis	[101]
Matrix mechanics	Stiff matrix	Huh7/Hepa1-6 tumor cells	Tumor cells/tissues	Enhanced tumor growth via EV-mediated Notch signaling	Hepatocellular carcinoma growth	[95]

ADSCs: adipose-derived stem cells; BMSCs: bone marrow-derived mesenchymal stem cells; BMECs: bone marrow endothelial cells; EPCs: endothelial progenitor cells; EndoMT: endothelial-to-mesenchymal transition; EV: extracellular vesicle; EVs: extracellular vesicles; HCC: hepatocellular carcinoma; HUVECs: human umbilical vein endothelial cells; IL-1 β : interleukin-1 beta; LSS: laminar shear stress; M1: classically activated macrophages; M2: alternatively activated macrophages; NF- κ B: nuclear factor kappa B; ROS: reactive oxygen species.

thereby reducing local inflammation^[72]. In the context of tissue repair, Dai *et al.* reviewed how biochemical and biophysical microenvironments influence EV production, cargo and therapeutic activity^[148]. They proposed that donor-cell preconditioning may act through EVs to regulate inflammation resolution, cell migration, angiogenesis and extracellular matrix remodeling^[148].

Adaptive and pathogenic effects under excessive or pathological mechanical stress

Pathological or excessive mechanical loading does not invariably produce harmful EV-mediated effects. During compensatory stages, EVs may contribute to systemic adaptation to mechanical stress. For example, cardiac pressure overload can promote the release of EVs carrying functional angiotensin II type 1 receptors (AT1R) into the circulation^[102]. These EVs transfer AT1R to peripheral tissues, increasing recipient-cell responsiveness to angiotensin II^[102]. This study suggests that EVs may support long-range hemodynamic coordination during pressure overload, linking local cardiac stress to systemic adaptive responses.

Abnormal, excessive or sustained mechanical stimulation can instead promote EV-mediated amplification of inflammation, calcification and tissue injury. Disturbed flow is associated with endothelial MAPK activation and increased release of pro-inflammatory EVs. The isolated EVs can promote macrophage polarization towards the classically activated macrophage (M1) phenotype and foam cell formation, providing direct evidence that they convey pro-inflammatory activity^[15]. Oscillatory shear stress can also activate secretory autophagy and promote lysyl-tRNA synthetase 1 loading into EVs. These EVs transmit inflammatory signals within the local vascular environment and exacerbate endothelial dysfunction^[46]. Interstitial fluid shear stress is associated with epidermal growth factor receptor-MAPK-Krüppel-like factor 5 (KLF5) activation, a shift towards the synthetic phenotype in vascular smooth muscle cells, and pro-calcific EV release^[42]. Cyclic stretch increased caveolin-1 content and the mineralization potential of vascular smooth muscle cell-derived EVs- in a cell-free high-phosphate assay^[79].

A stiffened tumor microenvironment can likewise promote tumor growth and distant metastasis through EVs. In hepatocellular carcinoma models, high matrix stiffness can promote the enrichment of let-7d-5p and miR-365a-5p in tumor-cell-derived EVs. EV transfer and cargo perturbation experiments support two complementary mechanisms of action^[101]. Let-7d-5p suppresses glucose uptake by lung fibroblasts through the high mobility group AT-hook 2/E2F transcription factor 1 axis, whereas miR-365a-5p promotes angiogenesis and vascular permeability through the transient receptor potential cation channel subfamily C member 4-associated protein-Ca²⁺-extracellular signal-regulated kinase 5 axis^[101]. Together, these effects create a pulmonary pre-metastatic niche that favors tumor colonization.

CHALLENGES AND FUTURE DIRECTIONS

The mechanotransduction-extracellular vesicle axis: limitations of current evidence and challenges in causal attribution

Current evidence favors a context-dependent spectrum of functions rather than two stable, independent EV subtypes. Whether mechanically remodeled EVs exert protective or pathogenic effects depends on stimulus type, intensity, frequency and duration. These effects are also shaped by donor-cell source and disease state, EV subpopulation and cargo composition, recipient tissue and disease stage. Studies of the vascular system provide a relatively clear comparison. EVs associated with atheroprotective laminar flow generally show anti-inflammatory effects^[16]. By contrast, EVs associated with disturbed flow or oscillatory shear can promote endothelial activation, macrophage inflammation, and vascular calcification^[15,46]. EVs thus tend towards

protective effects under physiological conditions and pathogenic effects under pathological conditions. However, this dose-dependent, bidirectional model is largely inferred by synthesizing findings across different experimental systems. Comprehensive dose-time comparisons using matched donor cells, recipient cells, and EV assessment protocols remain lacking.

Mechanical stimulation can also directly activate cellular signaling and alter soluble-factor secretion, so associated phenotypes cannot automatically be attributed to EVs. EV-dependent effects must therefore be distinguished from those arising through EV-independent mechanisms^[19]. For example, in a stiffened tumor microenvironment, the Piezo-type mechanosensitive ion channel component 1 (Piezo1)-Ca²⁺-calcium/calmodulin-dependent protein kinase II-cAMP response element-binding protein 1-odd-skipped related transcription factor 2 (OSR2) pathway can directly drive cluster of differentiation 8-positive (CD8⁺) T-cell exhaustion^[149]. Tumor-derived EVs can also promote this phenotype through signaling associated with the type II TGF- β receptor^[150]. To resolve the EV contribution, cell-type-specific, inducible perturbations of ras-related protein Rab-27A and ras-related protein Rab-27B (RAB27A/B) or sphingomyelin phosphodiesterase 3 (SMPD3) can be combined with EV-depleted fractions, non-EV fractions and purified-EV add-back experiments^[19,26,151,152]. Existing studies have mainly used GW4869 and EV-depleted conditioned medium to assess the contribution of EVs to observed phenotypes^[152]. Of the 98 studies included in this review, only 11 (11.2%) used at least one strategy to test EV involvement or provide a critical control. Eight used GW4869^[41,55,62,63,72,85,103,105], five included EV-depleted conditioned medium^[41,47,53,72,101], and two used both approaches^[41,72]. Attenuation of a phenotype after inhibiting EV release, followed by restoration after EV add-back, supports EV involvement in the causal process but does not alone establish causality. Neither GW4869 treatment nor perturbation of RAB27A/B or SMPD3 can specifically and comprehensively suppress all EV subpopulations^[19,26,151]. More reliable attribution therefore requires independent genetic and pharmacological perturbations, controls for cell viability and proliferation, EV subpopulation characterization and non-EV controls. Together, these approaches can help estimate the specific contribution of mechanically remodeled EVs.

Among the included studies, we found no specific biomarker, signaling profile or functional signature that consistently distinguished mechanically remodeled EVs from baseline EVs across experimental contexts. Such discrimination has not been established across mechanical stimulus types, donor cells and tissue environments. This evidence gap reflects both the limited number and statistical power of available studies and their predominant focus on individual stimuli or donor-cell sources. Future work should compare multiple stimuli and cell sources over time using standardized culture, EV isolation and detection protocols. Reproducible combinations of markers should then be validated in independent cohorts.

Local and distant effects of mechanically remodeled EVs: potential feedback regulation

Mechanically remodeled EVs can act on locally damaged tissues or reach distant sites through interstitial fluid or the circulation. Their range of action depends on extracellular matrix retention, clearance *in vivo*, tissue tropism, and recipient-cell uptake^[153-155]. Locally, endothelial small EVs induced by laminar shear can suppress inflammation, whereas EVs induced by oscillatory shear promote endothelial activation, apoptosis, and monocyte adhesion^[43]. EVs from endothelial cells exposed to tensile stress can also convey YAP/TAZ-Notch1/Dll4-associated signals, promoting H-type endothelium formation and tissue regeneration^[75]. At distant sites, cardiac pressure overload can promote the entry of EVs carrying functional AT1R into the circulation. When administered exogenously, these EVs can transfer AT1R to peripheral tissues and restore the blood pressure response to angiotensin II in AT1R-deficient mice^[102].

These local and distant effects provide a basis for investigating EV-mediated feedback in mechanical responses, but do not establish a closed feedback loop. Potential feedback could arise through direct EV effects on donor cells or indirectly through neighboring cells that remodel the local microenvironment.

However, direct evidence that these effects alter donor-cell mechanosensitivity or subsequent EV release remains limited. Future studies should combine spatiotemporally resolved EV tracking with validated interventions targeting EV release or uptake. These approaches should be coupled with dynamic monitoring of mechanical responses in donor cells and local tissues. Such experiments could test whether EVs establish direct or indirect feedback loops and distinguish feedback regulation from unidirectional paracrine signaling. They could also determine whether these loops support adaptive regulation or reinforce pathological responses.

Multiscale network analysis: towards data-driven virtual cell models.

EV-mediated mechanotransduction forms a multiscale network linking mechanical parameters and donor-cell mechanosensing to EV biogenesis, cargo selection, release, and recipient-tissue responses. Artificial intelligence (AI)-based virtual cells are multimodal computational models that can learn and simulate cellular state transitions under perturbation, offering a predictive framework for examining this complexity^[156]. EV-focused virtual cell models could integrate calibrated mechanical parameters with membrane-trafficking dynamics captured by live-cell imaging. Additional inputs could include donor-cell multi-omics data, single-EV molecular profiles, release kinetics, and recipient-cell phenotypes. This integration could enable *in silico* testing of whether specific mechanical environments preferentially alter EV quantity, cargo, or function. However, current virtual cell models mainly predict transcriptomic responses to genetic or chemical perturbations. They do not yet capture EV heterogeneity, vesicle trafficking, or force-dependent membrane dynamics. Progress will therefore require standardized protocols for mechanical stimulation and electrophysiological characterization, interoperable metadata and longitudinal multimodal datasets. Cross-laboratory benchmarking and prospective experimental validation will also be needed to assess model performance. Virtual cell models should serve as digital counterparts for generating hypotheses, not as substitutes for mechanistic experiments.

Connecting mechanical force, EVs, and disease: universal rules or specific functions

All cell types and tissues in the body exist within a specific mechanical microenvironment, and an imbalance in the steady state of this microenvironment can trigger a series of pathological cascade reactions, thereby participating in the occurrence and progression of various diseases. Abnormal mechanical signaling is now recognized as a key driver of diverse pathologies, including pulmonary fibrosis^[6], tumors^[6,157], and stroke^[158]. Notably, this regulatory axis extends to eye diseases such as retinal artery occlusion^[159-162] and glaucoma^[163,164]. However, in the process of the occurrence and development of ocular pathologies, how directional changes in the mechanical microenvironment regulate the secretion, composition, and function of EVs, and thus affect the evolution trajectory of diseases, currently lacks clear understanding, and the relevant regulatory mechanisms urgently need further systematic clarification and in-depth exploration.

In conclusion, it is imperative to establish quantitative correlations between mechanical parameters and EV phenotypes. Clarifying these context-dependent regulatory patterns will facilitate the development of standardized regulatory systems, ultimately enabling the precise translation of mechanobiological research into personalized clinical therapies.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the conception and design of the study: Hu L, Xiao X

Data curation: Wang A, Xu H, Liu H, Yang A, Zhu R

Writing - original draft: Wang A, Xu H

Writing - review & editing: Hu L, Xiao X, Yan B, Wang N, Wang A

Availability of data and materials

Not applicable.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool DeepSeek (version 3.2, released 2025-12-01) was used solely for language editing. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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