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Review

Extracellular vesicles originating from the mechanical microenvironment in the pathogenesis and applications for cardiovascular diseases

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ABSTRACT

The mechanical microenvironment plays a crucial regulatory role in the growth and development of cells. Mechanical stimuli, including shear, tensile, compression, and extracellular matrix forces, significantly influence cell adhesion, migration, proliferation, differentiation, and various other cellular functions. Extracellular vesicles (EVs) are involved in numerous physiological and pathological processes, with their occurrence and secretion being strictly regulated by the mechanical microenvironment. Recent studies have confirmed that alterations in the mechanical microenvironment are present in cardiovascular diseases, and the components of EVs can respond to changes in mechanical signals, thereby impacting the progression of these diseases. Additionally, engineered EVs, created by leveraging mechanical microenvironments, can serve as natural drug-delivery vehicles for treating and managing specific diseases. This article systematically reviews the regulatory mechanisms through which the mechanical microenvironment influences EVs and summarizes the role and advancements of EVs derived from this environment in the context of cardiovascular diseases.

Contents

Abbreviations: EVs, Extracellular vesicles; ILVs, intraluminal vesicles; MVBs, multivesicular bodies; FSS, fluid shear stress; IFSS, interstitial fluid shear stress; ECM, extracellular matrix; VEGFR2, Vascular Endothelial Growth Factor Receptor 2; vWF, von Willebrand factor; TGF-β, transforming growth factor-β; AS, atherosclerosis; WSS, low wall shear stress; CAD, coronary artery disease; SACs, stretch-activated channels; ERK, Extracellular Signal Regulated Kinase; ROS, reactive oxygen species; PGs, proteoglycans; GAGs, glycosaminoglycans; ESCRT, Endosomal Sorting Complex Required for Transport; VPS4, vacuolar protein sorting 4; VTA1, vesicle trafficking 1; ALIX, ALG-2-interacting protein X; RAB, targeting GTPase; GPR143, G protein-coupled receptor 143; EGFR, epidermal growth factor receptor; PM, plasma membrane; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; miRNA, microRNA; RBPs, RNA-binding proteins; KLF2, krüppel-like factor 2; FAK, focal adhesion kinase; PI3K, phosphoinositide 3-kinase; PTEN, tensin homolog; Akt, protein kinase B; Arp2/3, actin-related protein-2/3; PI(3,5)P2, phosphatidylinositol-3,5-bisphosphate; TTLL4, tubulin tyrosine ligase-like 4; YAP, Yes-associated protein; TAZ, tafazzin; CAVIN1, caveolae-associated protein 1; TRPV4, Transient receptor potential vanilloid 4; TECs, tumor endothelial cells; PD-L1, the programmed cell death 1 ligand 1; PPARα, peroxisome proliferator-activated receptor α; NF-κB, nuclear factor kappa-B; MYD88, myeloid differentiation primary response protein 88; NLRP3, nucleotide-binding oligomerization domain-like receptor protein 3; ABCA1, ATP-binding cassette transporter A1; IL, interleukin; TNF-α, tumor necrosis factor-α; TGFBR3, transforming growth factor beta receptor 3; JNK, c-Jun N-terminal kinase; LSS, laminar shear stress; OSS, oscillatory shear stress; BMP, bone morphogenetic protein; SMAD, drosophila mothers against decapentaplegic protein; EDN1, Endothelin 1; ALK1, anaplasticlymphoma kinase 1; VSMCs, vascular smooth muscle cells; MAPK, mitogen-activated protein kinases; KLF5, krüppel-like factor 5; EPCs, endothelial progenitor cells; hiPSC, human induced pluripotent stem cell; PIEZO1, piezo-type mechanosensitive ion channel component 1; cAMP, cyclic adenosine monophosphate; AT1R, angiotensin II type 1 receptor; MSCs, mesenchymal stem cells; BM, bone marrow; TFF, tangential flow filtration; SRSF1, serine and arginine rich splicing factor 1; AMPK, adenosine 5′-monophosphate-activated protein kinase; I/R, ischemia/reperfusion; ADSC, adipose-derived stem cells; T2DM, model of type 2 diabetes; VCAM, vascular cell adhesion molecule; MCP1, monocyte chemotactic protein-1.

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1. Introduction

Cardiovascular disease is among the most prevalent diseases globally. Conditions such as myocardial infarction and atherosclerosis, along with other acute and chronic cardiovascular diseases, continue to exhibit high morbidity and mortality rates. Extracellular vesicles are membranous structures derived from the endosomal system of cells, primarily categorized into exosomes and microvesicles [1]. EVs are formed from endosomes; during the transition from early to late endosomes, the membrane undergoes indentation and budding to create intraluminal vesicles (ILVs). Many ILVs aggregate to form multivesicular bodies (MVBs), which can interact with cell membranes and facilitate the release of EVs outside the cell through exocytosis [2]. The diameter of EVs typically ranges from 30 nm to 120 nm and is closely associated with various biological activities, including intercellular communication, reproductive development, infection, and immune responses [3]. In recent years, numerous studies have demonstrated that EVs can regulate the onset and progression of cardiovascular diseases and have been utilized in clinical treatments [4]. EVs are abundant in diverse proteins, lipids, mRNA, and non-coding RNA, collectively reflecting the functional status of the parent cell and its physiological and pathological information [3,5]. Research indicates that several key cell types involved in the progression of cardiovascular diseases, such as cardiomyocytes, endothelial cells, and smooth muscle cells, exhibit significant differences in the EVs released during disease states compared to normal conditions [6,7]. This disparity provides a foundation for the early identification and evaluation of treatment effects in cardiovascular disease, thereby opening new avenues for research.

The mechanical microenvironment refers to how cells perceive surrounding mechanical stimuli. In living organisms, the primary mechanical stimuli include but are not limited to, hydrostatic pressure, fluid shear stress, tensile forces, and the hardness and viscosity of the extracellular matrix [8]. For instance, under physiological laminar flow conditions, endothelial cells in blood vessels can maintain a stable state [9]; however, alterations in the mechanical microenvironment, such as changes in hemodynamics and pressure on the blood vessel wall, can activate the endothelium, promoting its proliferation and migration, which contributes to the development of cardiovascular diseases. For example, oscillatory shear stress induces endothelial cell polarity changes linked to atherogenesis [10]. Additionally, increased pathological tensile stress can enhance autophagy flux in vascular smooth muscle cells, thereby promoting the progression of hypertension [11]. Nonetheless, the mechanisms by which abnormal physical stress leads to cardiovascular disease remain incompletely understood. It is, however, clear that EVs released by cardiovascular tissue cells within this mechanical microenvironment play a crucial regulatory role in the onset of cardiovascular diseases.

This review aims to analyze the mechanisms by which the mechanical microenvironment regulates EVs and their implications for the development of cardiovascular diseases and potential therapeutic applications. Furthermore, we will explore the advancement of engineered EVs to achieve efficient and precise treatment of cardiovascular conditions.

2. Basic introduction to the mechanical microenvironment

The cell microenvironment encompasses various factors that influence and regulate cellular life processes, with the mechanical microenvironment specifically referring to the mechanical stimuli that impact cell growth and development. The cytomechanical microenvironment typically includes hydrostatic pressure, fluid shear stress (FSS), tensile force, extracellular matrix (ECM) stiffness or tissue elasticity, and extracellular fluid viscosity [8,12] (as shown in Fig. 1).

Fluid shear stress can be categorized into low shear stress and high shear stress based on the magnitude of the mechanical effect, as well as into laminar shear stress and oscillatory shear stress according to different fluid states. In the body, fluid shear stress is predominantly generated within the lumen, where endothelial cells exhibit heightened sensitivity to changes in force. Shear stress in blood vessels can promote the formation of vascular collateral circulation and mitigate the adverse effects associated with vaso-occlusive diseases. Under shear stress, extracellular RNA released by endothelial cells interacts with vascular endothelial growth factor receptor 2 (VEGFR2), regulating leukocyte recruitment and von Willebrand factor (vWF) release, thereby initiating arteriogenesis and arterial inflammation [13]. However, the physiological structure of blood vessels, including bends and proximal branches, renders these regions more susceptible to low shear stress or oscillatory shear stress from blood flow, often resulting in endothelial cell damage and thrombosis. The functional state of endothelial cells is closely linked to fluid shear stress; under physiological conditions, they exist in a laminar flow environment characterized by high shear stress, maintaining a stable state [9]. In contrast, endothelial cells experience low shear stress under pathological conditions, leading to disrupted functions in disturbed flow conditions [14]. This disruption may be attributed to activating the transforming growth factor-β (TGF-β) signaling pathway [15].

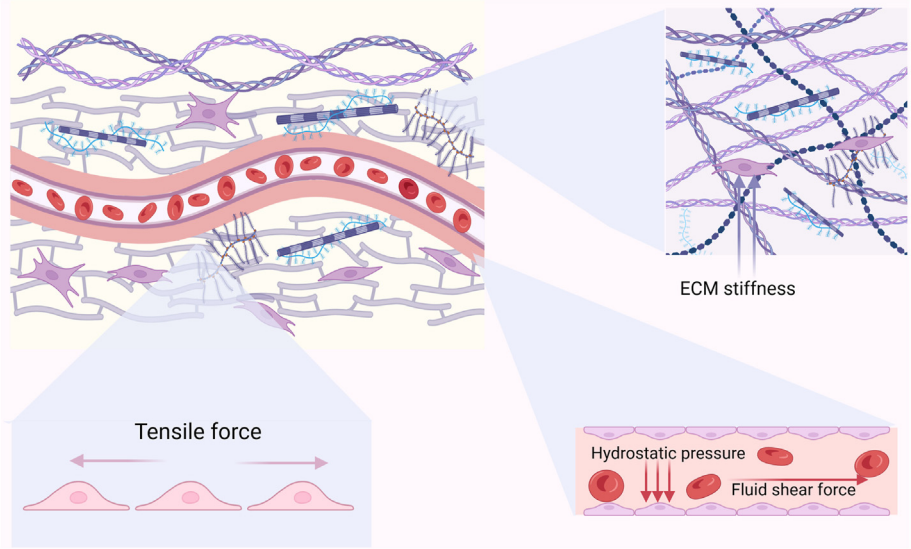

Fig. 1. Fundamental biological forces operate within the microenvironment. The extracellular matrix constitutes a complex network of proteins, proteoglycans, and glycoproteins. Hydrostatic pressure is prevalent in fluid-containing tissues and organs, such as blood vessels. Blood flow within the human vasculature generates characteristic fluid shear forces. Tensile forces play a crucial role in muscle and joint movement, atherogenesis, cardiovascular remodeling, and various cellular activities.

Consequently, vessel curvatures and proximal branches are primary sites for developing atherosclerotic lesions. Plaque erosion is a significant factor in the progression of atherosclerosis (AS). Recent research indicates that in AS, plaque erosion within narrow vascular lumens is associated with endothelial shear stress [16]. Furthermore, low wall shear stress (WSS) and oscillatory shear stress contribute to plaque formation. The former is known to induce large-scale plaque lesions that exhibit high brittleness, while the latter is associated with developing relatively stable plaques [17]. Measuring WSS at the proximal lesion site can effectively monitor hemodynamic changes in patients with stable coronary artery disease (CAD) and predict the risk of myocardial infarction. Additionally, some studies suggest that fluid shear stress is closely related to the release of EVs [18] and can also regulate the composition of these EVs, thereby influencing the function of target cells [19].

Tensile and compressive forces are typically generated simultaneously. Research indicates that nearly all types of mechanical stress can activate stretch-activated channels (SACs) on the cell membrane. The activation of SACs can lead to cytoskeletal remodeling, adjustments in cell growth and survival, and the expression of apoptosis-related genes [20]. Studies have demonstrated that under conditions of cardiac pressure overload, cardiomyocytes subjected to osmotic stretch forces can trigger blood pressure responses and cardiac extracellular signal-regulated kinase (ERK) signaling by inducing an angiotensin II response, thereby maintaining pathologies such as hypertension and heart failure [21]. Furthermore, in coronary artery bypass grafting studies, sustained high tensile stress has been shown to increase the generation of reactive oxygen species (ROS) in endothelial cells, accompanied by actin cytoskeletal remodeling. This remodeling contributes to saphenous vein endothelial cell dysfunction and slows the remodeling rate of the arterialized saphenous duct [22].

Additionally, the stiffness and viscosity of the ECM are critical factors that shape the mechanical microenvironment. The ECM is composed of numerous proteins, including collagen, elastin, fibronectin, laminin, and other glycoproteins, as well as proteoglycans (PGs) and glycosaminoglycans (GAGs) [23]. Variations in ECM components can alter its hardness and viscosity, thereby influencing cell growth, proliferation, migration, differentiation, adhesion, and other processes [24]. Moreover, mechanical forces can also regulate the release of related factors in the ECM, impacting the physiological activities of cells.

3. The impact of mechanical microenvironment on the composition and release of EVs

A substantial body of research has demonstrated that EVs play a critical role in intercellular communication[25–27]. They can directly deliver molecules with specific functions to recipient cells, facilitating information transmission. EVs primarily consist of proteins, nucleic acids, and lipids. During their formation, cells internalize endosomes to create vesicles, a process regulated by various proteins. The classic pathway for EVs production is the Endosomal Sorting Complex Required for Transport (ESCRT) pathway. This pathway comprises multimeric complexes—ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III—as well as cofactors such as vacuolar protein sorting 4 (VPS4), vesicle trafficking 1 (VTA1), and ALG-2-interacting protein X (ALIX), which collaborate in a coordinated manner [28]. Non-canonical pathways have also been identified as regulators of protein sorting in EVs. The targeting GTPase-31 (RAB31) protein is crucial for marking and regulating the formation of EVs, promoting the development of ILVs while inhibiting the fusion of MVBs with lysosomes [29]. The mechanisms by which luminal determinants contribute to the formation of ILVs involve the secretion of EVs containing the Pmel17 protein [30]. Furthermore, G protein-coupled receptor 143 (GPR143) has been shown to interact with HRS, enhancing its binding affinity to specific proteins such as epidermal growth factor receptor (EGFR) and facilitating the sorting of ILVs [28]. The formation of intracellular MVBs for EVs release involves three key steps: the transport of MVBs, the docking of MVBs, and their fusion with the plasma membrane (PM) [31]. The Rab GTPase protein family, the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein family, and cytoskeletal proteins play significant roles in these processes.

Cells residing in distinct mechanical microenvironments secrete EVs that exhibit significant variations in composition. The mechanisms underlying the sorting of proteins into EVs remain an area requiring further investigation. Additionally, the mechanical

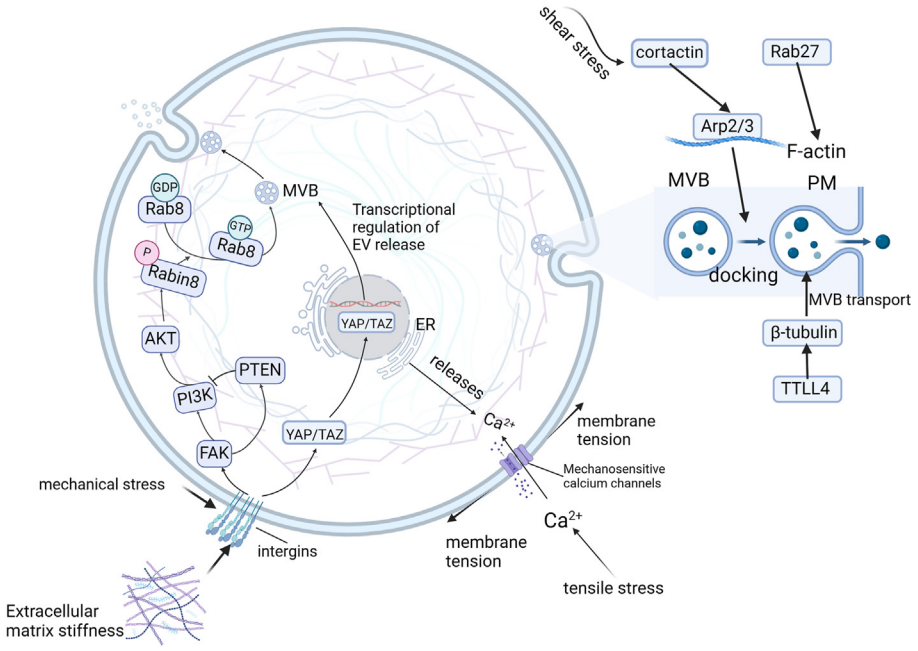

Fig. 2. The mechanical microenvironment plays a crucial role in regulating the mechanism of EVs release. In conjunction with cytoskeletal proteins, the extracellular matrix and integrins influence the fusion and release of MVBs and the plasma membrane by activating the transcription of YAP/TAZ and the PI3K/AKT pathway. Under mechanical stimulation, Ca^{2+} ions traverse activated mechanical channels, thereby regulating secretory vesicles within the endoplasmic reticulum. Additionally, shear force modulates cytoskeletal proteins by activating Rab proteins, subsequently impacting the fusion of MVBs with the plasma membrane.

microenvironment can induce alterations in exosomal RNA, particularly microRNA (miRNA). The sorting of miRNA into EVs primarily occurs through interactions with RNA-binding proteins (RBPs)[32–34] and is also influenced by membrane proteins associated with EVs biogenesis [35–37]. Numerous studies have identified various mechanically induced miRNAs by sequencing exosomal miRNAs. Following mechanical stimulation, the expression levels of these miRNAs in EVs are altered, thereby impacting cellular functions [19,38]. Concurrently, the mechanical microenvironment can modulate the expression of cytoskeleton-related proteins, regulate ion channels on the cell membrane, and subsequently influence the transport of MVBs as well as their docking and fusion with the plasma membrane, ultimately affecting the release of EVs (as shown in Fig. 2).

3.1. Rab GTPase protein family and EVs release

The Rab GTPase protein family comprises small GTPases that belong to the Ras superfamily and play a critical role in regulating intracellular metabolism. They coordinate the biogenesis, transport, docking, and fusion of membrane-containing organelles and vesicles [39]. In a study conducted by M. Ostrowski et al. [40], it was demonstrated that two GTPases, Rab27a and Rab27b, are essential for mediating the fusion of MVBs and the PM to facilitate EVs release. In different cellular contexts, the same Rab protein can perform distinct functions. For instance, Rab27a is essential for the secretion of EVs in HeLa cells; however, in endothelial cells, the shear stress-responsive transcription factor Krüppel-like factor 2 (KLF2) promotes the secretion of miR-143 EVs independently of Rab27a [41]. Furthermore, when the ECM to which cells are anchored experiences mechanical stress, the cell membrane structure undergoes corresponding remodeling. The sclerosis of the ECM leads to the phosphorylation of focal adhesion kinase (FAK) while simultaneously downregulating the phosphoinositide 3-kinase (PI3K) antagonist phosphatase and tensin homolog (PTEN). This sequence of events ultimately activates the FAK/PI3K/protein kinase B (Akt) signaling pathway, in which the phosphorylated Rabin8 protein is activated, promoting the transport of MVBs to the cell periphery and accelerating EVs release [42].

3.2. Cytoskeletal proteins and EVs release

The mechanosensitive actin cytoskeleton and membrane caveolar structures play critical roles in dynamic processes such as cell migration, morphology establishment, and vesicle transport. Mechanical stimulation of cells triggers the reassembly of the intracellular actin skeleton. This remodeling process is often facilitated by the activation of signaling molecules, such as Rho family GTPases, which influence the cell's overall morphological structure and internal architecture [43]. As the primary mediator of mechanical signal transduction, the cytoskeletal system coordinates the distribution and dynamic balance of intracellular materials and serves as a crucial bridge for interactions between cells and their surrounding microenvironment.

The regulatory protein cortactin, associated with the actin cytoskeleton, plays a crucial role in promoting the secretion of EVs. In the context of cancer cells, cortactin directly influences EVs secretion. It precisely regulates the transport and delivery of MVBs by interacting with the actin-related protein-2/3 (Arp2/3) complex, the site of branched actin polymerization, and actin filaments. Furthermore, cortactin docks with the plasma membrane [44]. Additionally, the actin filament-binding domain of cortactin binds to phosphatidylinositol-3,5-bisphosphate (PI(3,5)P2), which exhibits competitive binding properties with actin filaments, leading to an antagonistic effect on cortactin and indirectly impacting exocytosis [45]. Concurrently, mechanical stress can regulate microtubules within cells, affecting the stability of the cytoskeleton, with tubulin further influencing EVs release. In breast cancer cells, the overexpression of tubulin tyrosine ligase-like 4 (TTLL4) significantly enhances the polyglutamylation of β-tubulin. In TTLL4-

overexpressing cells, there is a notable increase in the secretion of vesicles and MVBs [46].

Caveolae are concave invaginations of the cell membrane that respond to mechanical stimuli. The Hippo signaling pathway is a crucial mechanism for cellular response to mechanical stimulation, functioning primarily through the regulation of Yes-associated protein (YAP)/tafazzin (TAZ) transcription factors. YAP/TAZ can target and modulate the expression of two significant caveolae-related genes, Caveolin1 and caveolae-associated protein 1 (CAVIN1). These factors facilitate the formation of MVBs through endocytosis, which subsequently fuse with the plasma membrane to release EVs [47].

3.3. Ion channels and EVs release

Numerous ion channel groups are located on the cell membrane, and their activation status is likely closely related to the EVs release process. Mechanical stress can directly activate these ion channels, triggering the rapid flow of ions into and out of the cell and consequently altering intracellular ion concentrations. The activation status of these ion channels is intimately linked to the regulation of cell membrane tension. They may indirectly influence the EVs release process by affecting changes in the conformation of membrane proteins, with Ca^{2+} playing a critical role in this mechanism. Transient receptor potential vanilloid 4 (TRPV4) is a prevalent ion channel found in cell membranes. Localized Ca^{2+} enters cells through the TRPV4/caveolin-1 pathway [48].The mechanical microenvironment can downregulate the mechanosensitive ion channel TRPV4 in tumor endothelial cells (TECs) via EVs, thereby transforming normal endothelial cells into a tumor endothelial cell-like phenotype and promoting abnormal blood vessel formation [49]. Research evidence indicates that the programmed cell death one ligand 1 (PD-L1) protein can be transported to its functional site by diffusion to adjacent areas or via EVs. In mouse model experiments, the activity of Ca^{2+} channels has been demonstrated to regulate the release of EVs containing PD-L1, thereby influencing tumor growth [50].Additionally, shear stress can also affect ion channel proteins in cell membranes. Under shear stress, the piezo-type mechanosensitive ion channel component 1 (PIEZO1) ion channel on red blood cells can induce the production of EVs [51].

4. EVs and cardiovascular diseases in the mechanical microenvironment

EVs and cardiovascular diseases in the mechanical microenvironment. The inflammatory response plays a crucial role in the progression of cardiovascular diseases. Inflammation is frequently observed in conditions such as atherosclerosis, myocardial infarction, and hypertension [52,53]. Numerous studies have demonstrated that EVs can modulate inflammatory responses and contribute to advancing inflammatory diseases, including atherosclerosis, myocardial infarction, and hypertension [54]. EVs released from visceral adipose tissue contain miR-27b-3p, which infiltrates vascular endothelial cells and exacerbates the endothelial inflammatory response by downregulating the peroxisome proliferator-activated receptor α(PPARα) and activating nuclear factor kappa-B (NF-κB) signaling pathways, thereby facilitating the progression of atherosclerosis [55].

Additionally, the reduction of miR-182-5p in plasma EVs leads to the upregulation and activation of MYD88, which in turn activates the NF-κB/NLRP3 pathway in endothelial cells. This process enhances the pro-inflammatory effects of exosomes and contributes to the induction of atherosclerosis [56]. At the same time, EVs can also promote the development of atherosclerosis by influencing foam cell formation. EVs derived from fatty liver cells induce ATP-binding cassette transporter A1 (ABCA1) via miR-30a-3p, which mediates foam cell formation and accelerates the progression of atherosclerosis [57]. These studies indicate that EVs released from various cell sources can exert pro-inflammatory functions through the miRNAs they carry. However, some exosomal miRNAs also exhibit anti-inflammatory properties. For instance, EVs released from bone marrow-derived macrophages treated with interleukin 4 (IL-4) inhibit the NF-κB and tumor necrosis factor-α(TNF-α) signaling pathways, thereby suppressing inflammatory responses [58].

Additionally, the circ_0001785 molecule, present in EVs, competes for binding with miR-513a-5p, reducing its interaction with transforming growth factor beta receptor 3 (TGFBR3). This action mitigates endothelial cell damage and the formation of new blood vessels in plaques, ultimately delaying the progression of atherosclerosis [59]. These findings demonstrate that the regulatory effect of EVs on inflammation primarily depends on the RNA they contain. Consequently, in various cardiovascular diseases, the RNA produced under different mechanical microenvironments plays a crucial role in EVs disease regulation (as shown in Fig. 3, Table 1).

4.1. Physical stress and atherosclerosis

In AS, the intravascular shear force is intimately linked with the liberation of EVs. Shear stress can activate integrins, enhance their interaction with the Gα13 protein, and inhibit the activity of the transcription factor YAP. Consequently, this process limits the c-Jun N-terminal kinase (JNK) signaling pathway, downregulates pro-inflammatory genes, reduces the adhesion and infiltration of monocytes, inhibits inflammatory responses, and slows the progression of atherosclerosis [60]. Blood protective flow induces endothelial cells to express the shear-responsive transcription factor KLF2. KLF2 mediates EVs release by regulating the gene expression patterns of endothelial cells, thereby facilitating communication between endothelial cells and smooth muscle cells and delaying the progression of atherosclerosis [61]. Under the influence of atherosclerotic protective laminar shear stress (LSS) and pro-atherosclerotic oscillatory shear stress (OSS), the miRNAs derived from endothelial cell EVs are associated with angiogenesis, cell migration, and vascular inflammation. Notably, EVs produced under the influence of OSS can promote blood vessel formation, enhance cell migration, facilitate monocyte adhesion, and induce apoptosis, whereas EVs produced under LSS down-regulate the expression of pro-inflammatory genes [19]. Under the influence of OSS, endothelial progenitor cell-derived EVs can inhibit angiogenesis both in vivo and in vitro, promote endothelial-to-mesenchymal transition, and accelerate pathological vascular remodeling by delivering circular RNA (circ-1199) [62]. Additionally, FSS inhibits bone morphogenetic protein 9/10 (BMP9/10)-induced phosphorylation of drosophila mothers against decapentaplegic protein 1/5 (SMAD1/5) via Endoglin, and this phosphorylation can protect endothelial cells from the overexpression of the inflammatory marker Endothelin 1 (EDN1).

In contrast, under low shear stress, early endosomes enriched in Caveolin-1 facilitate the BMP9-Endoglin- anaplasticlymphoma kinase 1 (ALK1) pathway, leading to the accumulation of drosophila mothers against decapentaplegic protein (SMAD) in endothelial cells and the subsequent expression of mesenchymal and atherosclerotic genes [63]. In atherosclerotic arteries, vascular smooth muscle cells (VSMCs) experience increased interstitial fluid shear stress (IFSS) due to endothelial cell damage. IFSS promotes the transition of VSMCs from a contractile phenotype to a synthetic phenotype, exacerbating the formation of smooth muscle cell-derived foam cells. As IFSS stimulation intensifies, EGFR activates

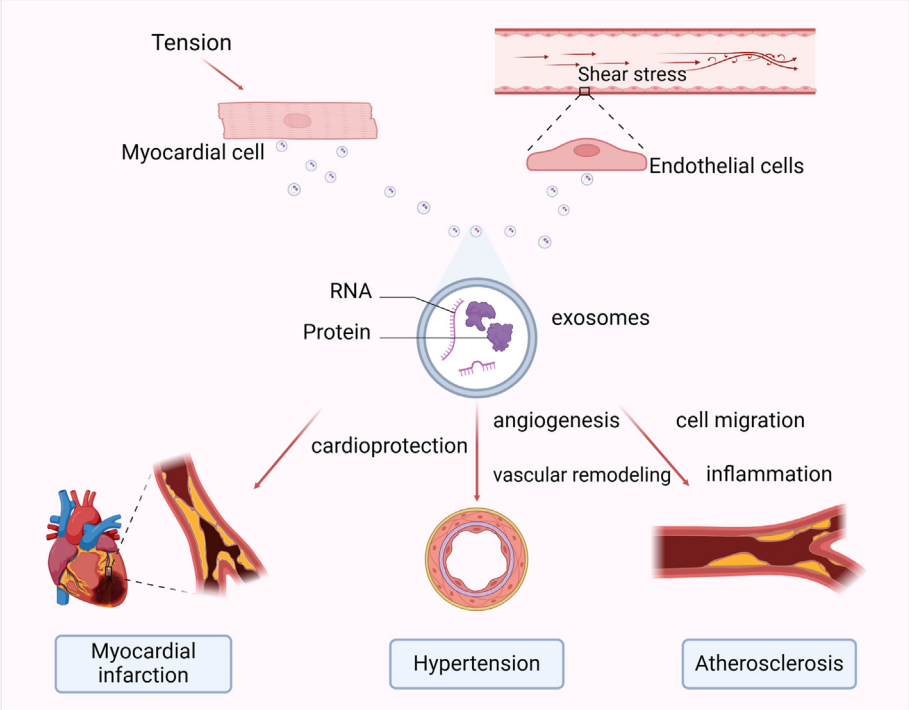

Fig. 3. EVs and cardiovascular diseases in the mechanical microenvironment. Endothelial cells and cardiomyocytes produce EVs that contain significant amounts of RNA and proteins when subjected to shear and stretch forces. These EVs can be delivered to target cells, exerting cardioprotective effects through angiogenesis, cell migration, inflammatory response, and vascular remodeling. Additionally, they regulate blood pressure and influence the progression of atherosclerosis.

Table 1
CVD -associated ncRNAs mentioned in AS and MI.

CVD	ncRNA	target gene/Pathway	Refs.
AS	miR-27b-3p	PPARα	[55]
	miR-182-5p	MYD88	[56]
	miR-30a-3p	ABCA1	[57]
	miR-99a/146b/378a	NF-κB/TNF-α	[58]
	circ_0001785	miR-513a-5p	[59]
	Circ-1199	Let-7g-5p	[62]
Myocardial infarction	miR-214-3p	PTEN	[65]
	miR-100-5p	Protein phosphatase β (PP-1β)	[67]
	miR-22-3p	Acyl-CoA synthetase long-chain family member 4 (ACSL4)	[68]

the mitogen-activated protein kinases (MAPK) signaling pathway, which promotes the nuclear accumulation of krüppel-like factor 5 (KLF5), enhances the release of EVs, and subsequently contributes to vascular calcification [64].

4.2. Myocardial infarction

EVs, nanoscale vesicles derived from the organism, play a crucial role in cardiac protection and repair. In a rat model of acute myocardial infarction, miR-214-3p within EVs can target PTEN and activate the *p*-AKT signaling pathway, thereby reducing the apoptosis rate of cardiomyocytes, promoting angiogenesis in the infarct area and facilitating cardiac self-regulation [65]. In mice with myocardial infarction, the injection of shear-thinning hyaluronic acid hydrogel binds to endothelial progenitor cells (EPCs), reduces shear stress, and improves EPC engraftment and survival rates, which stabilizes the boundary zone of myocardial infarction, reduces adverse myocardial remodeling, and preserves myocardial biomechanical properties [66]. This effect may be associated with EVs produced by myocardial infarction-related cells. Studies indicate that EVs secreted by human induced pluripotent stem cell-endothelial cells (hiPSC-ECs) differentiated from hiPSCs contain miR-100-5p, which has the potential to repair damaged hearts post-myocardial infarction [67]. Additionally, miR-22-3p, abundant in cardiomyocyte-derived EVs, can also protect cardiac tissue by inhibiting the ferroptosis pathway [68]. In summary, EVs derived from cardiovascular-related cells in the mechanical microenvironment not only participate in the pathogenesis of cardiovascular disease but also offer new insights and directions for potential treatments.

4.3. Hypertension

Hypertension is a significant risk factor for myocardial infarction, characterized by turbulent blood flow, increased fluid shear stress, vascular remodeling, and endothelial dysfunction. Blood pressure regulation depends on the production of endothelial relaxation factors. The mechanosensitive cation channel PIEZO1 in endothelial cells can mediate fluid shear stress-induced release of adrenocortical hormones, which in turn activates the Gs-coupled receptor-mediated cyclic adenosine monophosphate (cAMP) signaling pathway, thereby regulating the production of endothelial nitric oxide, vascular tone, and blood pressure levels [69]. Additionally, in the context of the mechanical microenvironment, EVs can transport various proteins that play a role in blood pressure regulation. Cardiomyocytes subjected to tensile stress utilize β-arrestin2 to secrete EVs containing angiotensin II type 1 receptor (AT1R), which modulates the vascular response to neurohormonal stimulation [21].

5. Mechanical microenvironment and the application of EVs

EVs exhibit excellent biocompatibility, low cytotoxicity, immune inertness, and specific targeted delivery capabilities, allowing them to circulate in the body for extended periods. Consequently, EVs hold significant potential as ideal drug delivery carriers. Numerous studies have employed EVs derived from various cell sources to encapsulate and transport therapeutic agents, including chemotherapy drugs and neurotransmitters. However, the large-scale production, isolation, and purification of EVs, while ensuring their quality and stability, pose substantial challenges to their application.

Given that the mechanical microenvironment can influence EVs production, extensive research has focused on efficiently generating, extracting, and purifying EVs through mechanical methods. Some studies have utilized mechanical stimulation via microfluidic devices to enhance EVs secretion from mesenchymal stem cells (MSCs) derived from human fetal bone marrow (BM-MSCs), all while preserving the proliferation state of the stem cells [70]. Researchers have cultivated mesenchymal stem cells in scalable microcarrier-based three-dimensional cultures to optimize EVs production. EVs produced by mesenchymal stem cells in three-dimensional culture demonstrate superior characteristics to those from two-dimensional culture. When combined with tangential flow filtration (TFF), the production of EVs can be further enhanced [71]. Evidence suggests that treating peripheral blood with shear stress can significantly reduce hemolysis while improving the yield and purity of red blood cell-derived EVs [51]. Additionally, Rayleigh waves and shear horizontal waves have been shown to effectively concentrate EVs while maintaining the integrity of extracellular vesicle preservation [72].

6. Engineering modified mechanically responsive EVs and drug delivery

In recent years, EVs have emerged as a prominent area of research for their potential as drug carriers in the targeted treatment of specific cardiovascular diseases. Current studies examine the effects of naturally secreted EVs components on AS and explore the design of engineered EVs for targeted cardiovascular disease therapy. For instance, the targeted delivery of engineered interleukin-10 (IL-10) mRNA-rich EVs to macrophages within AS plaques has been shown to reduce atherosclerotic symptoms in ApoE−/− mice [73]. Another study indicated that engineered M2 macrophage-derived EVs, treated with 5-aminohexyl levulinate hydrochloride via electroporation technology, exhibit significant anti-inflammatory effects and can inhibit the progression of atherosclerosis [74]. Furthermore, research has demonstrated that LINC00174, a component of EVs released from vascular endothelial cells, interacts with serine and arginine-rich splicing factor 1 (SRSF1) to inhibit p53-mediated autophagy and apoptosis. This interaction regulates the transcription of cardiac proteins and blocks the activation of the Akt/adenosine 5′-monophosphate-activated protein kinase (AMPK) pathway, thereby preventing myocardial injury caused by ischemia/reperfusion (I/R). This study suggests that the engineering modification of EVs containing LINC00174 may represent a novel approach to treating myocardial infarction resulting from I/R [75].

EVs derived from adipose-derived stem cells (ADSC) exhibit significant anti-apoptotic effects in cardiomyocytes subjected to oxidative stress, thereby providing adequate protection for these cells [76]. Concurrently, in a mouse model of type 2 diabetes (T2DM) complicated by stroke, EVs derived from human umbilical cord blood CD133+ cells, particularly miR-126, have been shown to enhance the expression of Spred-1, vascular cell adhesion molecule (VCAM), and monocyte chemotactic protein-1 (MCP1), promoting myocardial capillary growth in vivo and facilitating blood vessel formation [77]. Furthermore, ischemic cardiomyopathy EVs secreted by induced pluripotent stem cells and their differentiated cardiomyocytes can be harvested in vitro, serving as a substitute for live ischemic cardiomyocytes in cell-free treatments for myocardial infarction. This approach significantly improves cardiac function following myocardial infarction and presents a promising new strategy for cell-free, personalized treatment of ischemic cardiomyopathy [78].

7. Summary and outlook

The mechanical microenvironment regulates the release of EVs by influencing cytoskeletal proteins and membrane surface ion channels. Additionally, it can affect the generation and sorting of EVs, which alters their composition and function. EVs are nanoscale vesicles secreted by various cell types that can transport a range of biological macromolecules, including proteins, nucleic acids, and lipids, for intercellular delivery. Consequently, they are considered ideal carriers for drug delivery [79]. Numerous studies have demonstrated that EVs modified in different ways can treat various diseases [80,81]. However, despite evidence from studies on models of atherosclerosis, ischemia-reperfusion, and myocardial infarction indicating that EVs derived under mechanical conditions can resist inflammation, inhibit autophagy, and promote angiogenesis—thereby effectively delaying the progression of cardiovascular diseases—the clinical application of engineered EVs in this context still faces several challenges. For instance, ensuring the quality and stability of EVs produced at scale and addressing the limitations of current EV isolation and purification technologies, which lead to significant variations in their composition, remain critical hurdles [82]. Therefore, exploring the stable production of EVs under mechanical regulation is of great significance for diagnosing and treating cardiovascular diseases.

Author contributions

YZ, XC, HL, MC and XZ designed the present manuscript. YZ drawn the manuscript. YW performed a literature search and selected the studies to be performed. YZ revised, including the manuscript. All authors contributed to the article and approved the submitted version.

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Declaration of competing interest

There are no conflicts of interest in this study.

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