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MINI-REVIEW

Cyclic stretch and oxidative stress induced miRNAs in vascular remodeling

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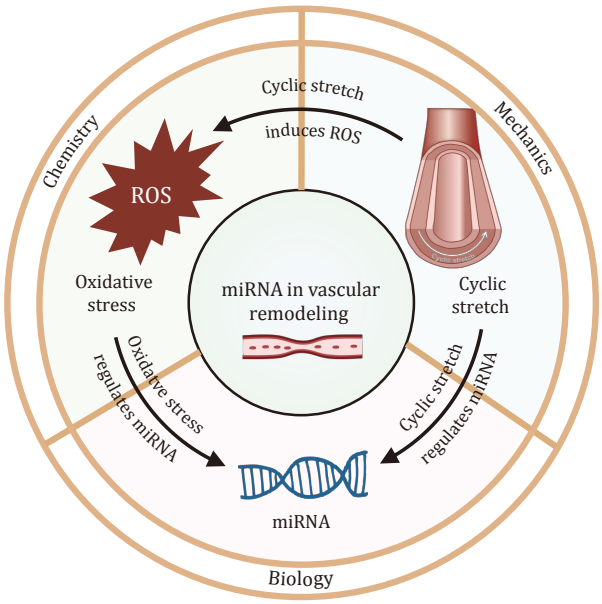
Graphical abstract



Abstract The 2024 Nobel Prize in Physiology or Medicine has reignited widespread enthusiasm and attention towards microRNA (miRNA). Recent advances have demonstrated that miRNAs serve as pivotal regulators in the process of vascular remodeling under conditions of cyclic stretch and oxidative stress. This mini-review introduced the brief history of miRNA research, summarized the roles of miRNAs in vascular diseases under cyclic stretch or oxidative stress, and discussed the potential research directions of miRNAs in redox biology and mechanobiology. Investigating the role of miRNAs under conditions of cyclic stretch and oxidative stress holds significant promise for advancing our comprehension of the fundamental mechanisms governing vascular biology, uncovering potential therapeutic targets, and facilitating the development of innovative treatment strategies for vascular diseases.

Keywords MicroRNAs (miRNAs), Cyclic stretch, Mechanotransduction, Oxidative stress, Reactive oxygen species (ROS), Vascular diseases

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INTRODUCTION

The brief history of miRNA research

Micro ribonucleic acids (microRNAs or miRNAs), typically comprising 21–23 nucleotides, are small, single-stranded, non-coding RNA molecules that play pivotal roles in post-transcriptional gene regulation (Lee *et al.* 1993; Wightman *et al.* 1993). The groundbreaking discovery of the first microRNA, lin-4, along with its mechanism of post-transcriptional regulation of the lin-14 gene, was elucidated through the pioneering works of Victor Ambros and Gary Ruvkun in 1993 (Lee *et al.* 1993; Wightman *et al.* 1993). The first microRNA responsive to mechanical stress was identified in 2005 in *Populus trichocarpa* (Huang and Qi 2024; Lu *et al.* 2005), a deciduous broadleaf tree species indigenous to western North America. Subsequently, in 2010, mechanosensitive miR-19a and miR-26a were discovered to play critical roles in human physiology and pathology, marking a pivotal advancement in understanding their biological significance (Huang and Qi 2024; Mohamed *et al.* 2010; Qin *et al.* 2010). Under conditions of oxidative stress, the repression of Cationic Amino Acid Transporter1 (CAT1) mRNA and/or reporter constructs containing fragments of its 3′ untranslated region (3′UTR) by miR-122 is alleviated in Huh7 cells (Bhattacharyya *et al.* 2006). This suggests that oxidative stress modulates the interaction between miR-122 and its target, potentially influencing cellular responses to stress (Bhattacharyya *et al.* 2006). In plants, miR-398 stands as the first microRNA identified to undergo transcriptional repression in response to oxidative stress in 2006 (Sunkar *et al.* 2006). This repression plays a key role in promoting the posttranscriptional accumulation of CSD1 and CSD2 mRNAs, thereby enhancing cellular tolerance to oxidative stress (Sunkar *et al.* 2006).

Overview of mechanical stress in the vascular system

Mechanical stress in the cardiovascular system refers to the forces exerted on the blood vessels, heart, and other components of the circulatory system. The mechanical environment plays a crucial role in maintaining the integrity and functionality of the cardiovascular system, while abnormal mechanical stress leads to various cardiovascular disorders (Cicalese *et al.* 2021; Green *et al.* 2017; Lacolley *et al.* 2017; Souilhol *et al.* 2020; Sugden *et al.* 2017; Wang *et al.* 2023). The mechanical stresses include shear stress, cyclic stretch, pressure and stiffness (Chien 2007; Davis *et al.* 2023; Herrera and Schwartz 2022). The heart undergoes cyclic stretch due to the nature of cardiac pulsations and blood vessels experience cyclic stretch as their walls rhythmically distend and relax in response to blood pressure imposed by heart propulsions. Physiological cyclic stretch is necessary for maintaining the structural integrity and function of cardiovascular tissues and organs, while excessive or abnormal cyclic stretch leads to hypertension, pulmonary hypertension (PH), ventilator -induced lung injury (VILI), and vein graft failure (Birukov 2009; Huang *et al.* 2017; Jiang *et al.* 2025; Qi *et al.* 2016; Tang *et al.* 2022; Wang *et al.* 2021).

The source of oxidative stress in the vascular system

Oxidative stress arises from a disruption in the delicate equilibrium between the generation and accumulation of reactive oxygen species (ROS) within cells and tissues, and the capacity of the biological system to neutralize and eliminate these reactive intermediates (Pizzino *et al.* 2017). Emerging research has demonstrated that the principal enzymatic generators of ROS within the cardiovascular system encompass NADPH oxidases (NOXs), uncoupled endothelial nitric oxide synthase (eNOS, also referred to as NOS3), mitochondrial electron transport chain, and xanthine oxidase (XO) (Ren *et al.* 2024; Zhang *et al.* 2020). Uncoupled eNOS produced excessive ROS to induce endothelial dysfunction (Huang *et al.* 2021a, b, 2022; Jiang *et al.* 2020; Youn *et al.* 2022). Existing studies have revealed that vascular and blood vessel related diseases involving oxidative stress include hypertension (Griendling *et al.* 2021; Guzik and Touyz 2017; Pokharel *et al.* 2023), aortic aneurysm (Huang *et al.* 2021a, b; Huang 2022; Zong *et al.* 2025), diabetic atherogenesis and atherosclerosis (Förstermann *et al.* 2017; Zhang *et al.* 2025), cerebrovascular disease (Chrissobolis and Faraci 2008), vein graft failure (Bai *et al.* 2017), varicose veins (Akar *et al.* 2018) and venous thromboembolism (Signorelli *et al.* 2020).

CYCLIC STRETCH-INDUCED miRNAs IN VASCULAR SYSTEM

In hypertension, high (pathological or abnormal) cyclic stretch induced miR-19b-3p downregulation, which led to connective tissue growth factor (CTGF) elevation, vascular smooth muscle cells (VSMCs) proliferation and vascular remodeling (Wang *et al.* 2019). In hypertensive rats, miR-124-3p-mediated downregulation of Lamin A/C plays a critical role in regulating VSMC

apoptosis under high cyclic stretch conditions (Bao *et al.* 2020). Elevated cyclic stretch (15%) also promotes miR-27a secretion from VSMCs, which transfers to endothelial cells (ECs) via VSMC-derived microparticles, targets GRK6, and drives EC proliferation. Notably, miRNA expression under different stretch conditions can appear contradictory, physiological stretching (5%) did not show this effect (Wang *et al.* 2017). Reducing local miR-27a levels may offer a new therapeutic strategy to curb pathological EC proliferation in hypertension (Wang *et al.* 2017). In cultured human aortic smooth muscle cells (HASMCs), elevated cyclic stretch enhances miR-21 expression through transcriptional activation, dependent on AP-1 (Song *et al.* 2012). miR-21 critically modulates stretch-induced cellular proliferation and apoptosis (Song *et al.* 2012). Interestingly, another study showed that high-intensity stretch (16%, 1 Hz) increases miR-21 expression in cultured HASMCs, whereas moderate stretch (10%, 1 Hz) reduces its expression (Song *et al.* 2012), which highlights the importance of mechanical context in miRNA regulation.

Upon grafting, veins are immediately subjected to arterial cyclic stretch due to the rhythmic deformation of the vessel wall under arterial blood pressure. Using the 'cuff' technique, vein grafts demonstrated progressive neointimal hyperplasia and enhanced cell proliferation over 1–4 weeks, accompanied by reduced miR-33 expression (Huang *et al.* 2017). Conversely, Bone Morphogenetic Protein 3 (BMP3, a miR-33 target) and its downstream effectors phosphorylated Smad2 and Smad5 (p-smad2/5) were upregulated (Huang *et al.* 2017). These findings reveal that the miR-33-BMP3-smad axis serves as a protective mechanism against venous VSMC proliferation induced by arterial cyclic stretch (Huang *et al.* 2017). miR-33 emerges as a promising therapeutic target for mitigating neointimal hyperplasia in vein grafts (Huang *et al.* 2017). Besides, arterial cyclic stretch upregulated miR-29a-3p expression, which mediated venous VSMC phenotypic transformation through the miR-29a-3p/TET1 signaling pathway (Liu *et al.* 2020). These findings suggest miR-29a-3p as a potential therapeutic target for vein graft restenosis (Liu *et al.* 2020). Furthermore, arterial stretch induced circSlc8a1 expression and the interaction between circSlc8a1 and miR-20a-5p, which upregulated Lamtor1, activated mechanistic target of rapamycin complex 1 (mTORC1), and promoted VSMC dedifferentiation and proliferation (Liu *et al.* 2022). The circSlc81/miR-20a-5p/Lamtor1 axis, induced by arterial stretch, represents a potential therapeutic target for neointimal hyperplasia in vein grafts (Liu *et al.* 2022). A summary of the key miRNAs and their regulatory networks involved in cyclic stretch-induced vascular remodeling is presented in Fig.1.

OXIDATIVE STRESS-REGULATED miRNAs IN VASCULAR PATHOPHYSIOLOGY

Extensive research has demonstrated that oxidative stress serves as a pivotal regulator in vascular remodeling, while miRNAs have been identified as crucial mediators in these pathophysiological processes (Huang *et al.* 2021a; Marin *et al.* 2013; Zampetaki *et al.* 2013; Zhang *et al.* 2020). Accumulating evidence from current research indicates that miRNAs serve as critical regulators in oxidative stress-mediated vascular remodeling, particularly in the pathogenesis of atherosclerosis and hypertension.

Atherosclerosis

The starting event of atherosclerosis is endothelial dysfunction. For ECs, oxidative stress activates innate immunity and destroys endothelial function, leading to endothelial dysfunction. In cultured human umbilical vein endothelial cells (HUVECs), oxidative stress induces miR-181a, directly inhibits the expression of B-cell lymphoma 2 (Bcl-2), leads to endothelial dysfunction, and promotes atherosclerosis (Liu *et al.* 2016). In mice, oxidative stress induced the upregulation of sterol regulatory element binding protein 2 expression, leading to the activation of miR-92a transcription, and then targeting key molecules in endothelial homeostasis, including sirtuin 1, Krüppel-like factor (KLF) 2 and KLF 4, to improve angiotensin-II (Ang II) induced and aging related atherogenesis (Chen *et al.* 2015). Oxidized low-density lipoprotein (ox-LDL)-induced vascular endothelial damage and oxidative stress play a vital role in the pathophysiology of atherosclerosis. In HUVECs, under oxidative stress caused by ox-LDL, elevated miR-21 reduces the expression of Phosphatase and Tensin Homolog deleted on chromosome 10 (PTEN), inhibits the expression of oxidative stress and inflammation, and alleviates atherosclerosis (Zhou *et al.* 2020). ox-LDL leads to upregulation of miR-497-5p, exacerbates ox-LDL induced HUVEC dysfunction through activation of the p38/MAPK pathway mediated by Vascular Endothelial Growth Factor A (VEGFA) targets (Lu *et al.* 2024). In addition, ox-LDL also inhibits miR-135a, leading to ROS accumulation, oxidative stress, and inflammatory response. Restoring miR-135a expression can inhibit oxidative stress, and Toll-like receptor 4 (TLR4) may be a target of miR-135a in this process (Du and Lu 2018).

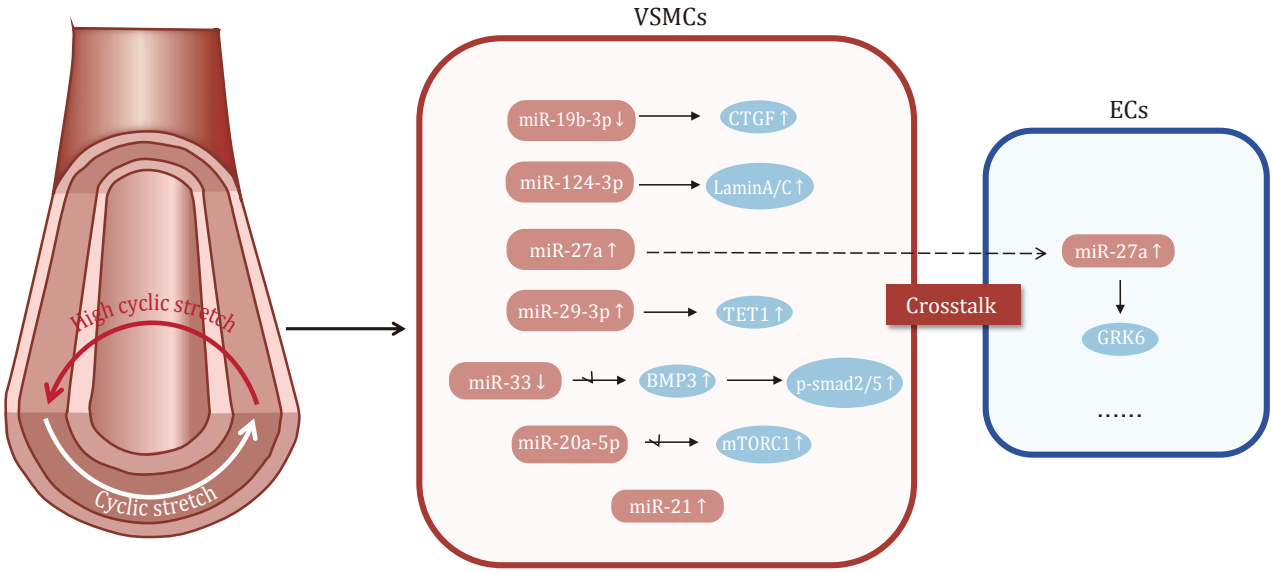

Fig. 1 Cyclic stretch-induced miRNAs and their regulatory roles in VSMCs and ECs. This figure summarizes key stretch-responsive miRNAs involved in vascular remodeling and their downstream targets. High cyclic stretch alters the expression of various miRNAs in VSMCs. Red boxes indicate changes in miRNA expression, while blue boxes represent downstream targets regulated by these miRNAs, ultimately affecting VSMC proliferation, apoptosis, and phenotypic switching. Certain miRNAs, such as miR-27a, mediate intercellular crosstalk by transferring to endothelial cells and modulating endothelial function

Hypertension

Vascular remodeling, primarily driven by the proliferation and migration of VSMCs, serves as the pathological basis of hypertension-associated vascular lesions. Oxidative stress promotes hypertension related DNA damage by upregulating Poly (ADP-ribose) polymerase 1 (PARP-1), while miR-103a-2-5p and miR-585-5p exacerbate this process by targeting PARP-1 inhibition (Dluzen *et al.* 2017). In spontaneously hypertensive rats, miR-31-5p exacerbates oxidative stress and VSMCs migration by directly targeting and suppressing Fibronectin type III domain-containing protein 5 (FNDC5) (Zhou *et al.* 2021). In the mouse model of atherosclerosis, miR-140-5p exacerbates hypertension and oxidative stress in atherosclerotic mice by suppressing the Nrf2/Sirt2/Keap1/HO-1 antioxidant pathway, thereby elevating ROS levels and aggravating vascular dysfunction (Liu *et al.* 2019). In addition, downregulated miR-22-3p in hypertensive vascular tissues exacerbates oxidative stress and vascular remodeling by targeting chromodomain helicase DNA-binding 9, which promotes synthetic phenotype switching in aortic smooth muscle cells (ASMCs) (Chen *et al.* 2021). Another study demonstrated that in reduced uterine perfusion pressure (RUPP)-induced rat models, upregulation of endothelial MALAT1 reduces endothelin-1 (ET-1) expression by competitively binding miR-150-5p. Conversely, ET-1 enhances endothelin B receptor (ETBR) expression via NF-κB pathway activation in SMCs, promoting oxidative stress imbalance and exacerbating hypertension in RUPP rats (Ou *et al.* 2020).

Other vascular diseases

Arterial aneurysms are mainly divided into thoracic aortic aneurysm (TAA) and abdominal aortic aneurysm (AAA) according to their location of occurrence. In both Ang II-induced AAA mice and oxidative stress-stimulated VSMC, oxidative stress drives AAA progression by upregulating lncRNA Sox2 overlapping transcript (Sox2-ot), which suppresses miR-145 and subsequently elevates Early growth response 1 (Egr1) expression. Conversely, restoring miR-145 or inhibiting Sox2-ot mitigates this pathological process (Lin *et al.* 2020). A recent study reveals that in a mouse model of AAA, Superoxide dismutase 2, mitochondrial (SOD2) mitigates disease progression by upregulating miR-181a-5p and miR-17-5p, thereby reducing vascular inflammation, suppressing apoptosis, and counteracting oxidative stress (Yan *et al.* 2025). Besides, we uncover the previously unrecognized role of miR-192-5p in driving ROS-mediated Dihydrofolate reductase (DHFR) loss and AAA pathogenesis (Huang *et al.* 2021a; Zong *et al.* 2025). Importantly, targeting this miRNA robustly attenuates aneurysm development, highlighting its translational relevance (Huang *et al.* 2021a; Zong *et al.* 2025).

Comparative analysis of miRNA expression profiles revealed that miR-224-5p, miR-206, and miR-653-5p were significantly dysregulated in thrombotic patients compared to healthy controls (Emmi *et al.* 2022). These miRNAs showed strong correlations with leukocyte-derived ROS production and plasma lipid peroxidation, suggesting their potential involvement in oxidative stress regulation during thrombosis (Emmi *et al.* 2022). In the progression of PH, miR-663b is significantly upregulated in hypoxia induced pulmonary artery smooth muscle cells (PASMCs) and M1 macrophages. Overexpression of miR-663b promotes inflammation and oxidative stress in PASMCs, exacerbating PH progression (Ma *et al.* 2023).

Therapeutic potential of redox-sensitive miRNAs

The current research highlights miRNAs as pivotal molecular mediators governing vascular disease progression under oxidative stress conditions, particularly in atherosclerosis, hypertension, AAA, and PH. These oxidative stress-responsive miRNAs orchestrate vascular pathophysiology through multiple mechanisms, including regulating endothelial integrity, VSMCs phenotype transition, and inflammatory signaling cascades. These miRNAs, as key effectors linking redox imbalance and vascular remodeling, have become promising therapeutic targets for precision medicine interventions in cardiovascular diseases (CVDs) (Fig. 2).

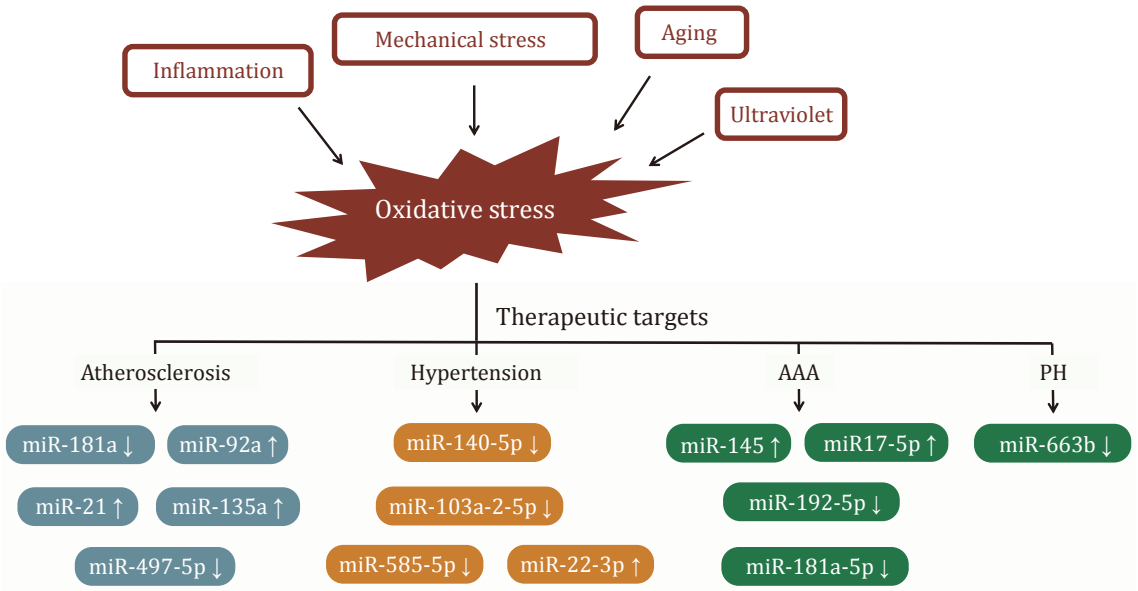

Fig. 2 Targeting miRNAs for CVDs treatment under oxidative stress. Oxidative stress, triggered by various stimuli such as inflammation, mechanical stress, aging, and ultraviolet radiation, plays a central role in vascular pathophysiology. It alters the expression of specific miRNAs that are critically involved in the progression of atherosclerosis, hypertension, AAA, and PH. This figure highlights representative oxidative stress-responsive miRNAs associated with each disease context. By affecting key vascular processes, these miRNAs offer potential for targeted therapies in CVDs

Notably, a single miRNA may exert both pro- and anti-disease effects within the same pathological context. For instance, miR-21, miR-126, and miR-155 exhibit dual roles in atherosclerosis, with their functions influenced by mechanical cues and downstream target specificity (Kumar *et al.* 2014). Moreover, the biological role of a given miRNA can differ across cardiovascular diseases. miR-155, for example, confers anti-inflammatory protection in heart failure models (Seok *et al.* 2014), but promotes inflammation and lesion progression in atherosclerosis (Zhang *et al.* 2015). These findings underscore the need to account for disease-specific and comorbidity-related functional heterogeneity when considering miRNAs as diagnostic or therapeutic targets.

NEW FRONTIERS AND UNDEFINED ROLES OF miRNAs IN MECHANOBIOLOGY AND REDOX BIOLOGY

While miRNA research – recognized by the Nobel Prize for its transformative insights into gene regulation –

has revolutionized molecular biology, the integration of miRNAs into mechanobiological and redox pathways lags behind. Current studies largely examine these pathways separately, and direct evidence linking stretch-induced ROS to miRNA regulation is scarce, underscoring a key gap for future investigation and a critical frontier for mechanobiology and redox biology research.

As central regulators of vascular remodeling, miRNAs are promising targets for CVD diagnosis and therapy, with therapeutic nanoparticle delivery emerging as a major focus (Park *et al.* 2020). Recent research demonstrates that nanoparticle-based delivery systems enable targeted manipulation of mechanosensitive miRNAs. Endogenous miR-146a serves a compensatory role during mechanical ventilation that partially limits injury. Delivery of miR-146a mimics via macrophage-targeted nanoparticles attenuates VILI by regulating mechanotransduction and inflammation (Bobba *et al.* 2024). Furthermore, redox-responsive nanoparticle platforms have been developed to selectively scavenge pathological ROS. Chen *et al*. intravenously administered nanoparticles surface-modified with ischemic myocardium-targeting peptides to deliver miR-199a-5p specifically to infarcted cardiac tissue, where it suppressed AGTR1 expression, reduced early-stage ROS accumulation, and promoted myocardial repair (Chen *et al.* 2024). These methods highlight the therapeutic potential of miRNA loaded nanoparticles in vascular remodeling. Despite progress, miRNA nanoparticle delivery remains limited by low efficiency, off-target effects, and the influence of cellular and microenvironmental context, highlighting the need for further optimization.

Beyond therapy, accurate diagnosis and prognosis of CVDs remain challenging. Conventional biomarkers (troponins, natriuretic peptides, and C-reactive protein) often indicate late-stage damage and lack specificity. In contrast, extracellular vesicle (EV)-bound miRNAs enable minimally invasive liquid biopsy with greater sensitivity for early detection and dynamic monitoring (Wang *et al.* 2025). For example, Ellis *et al*. established a microfluidic platform simulating human cardiac ischemia-reperfusion and integrated a rapid, extraction-free miRNA detection system, reproducing clinical miRNA expression patterns for early and sensitive myocardial infarction (MI) biomarker screening and validation (Ellis *et al.* 2022). Despite technical challenges in EV-miRNA standardization and comorbidity interference, EV-based liquid biopsy is considered a key direction in cardiovascular molecular diagnostics.

Given the insufficient research mentioned above, we propose areas that may be worth studying, including but not limited to: (1) The dual role of miRNA under mechanical stress and/or oxidative stress; (2) Gene transcriptional activation during mechanical stress and/or oxidative stress; (3) Mechanosensitive and oxidative stress-sensitive miRNA biomarkers for precision diagnosis of complex diseases; (4) The crosstalk between mechanical stress and oxidative stress in regulating miRNA; (5) Finding novel mechanosensitive and/or oxidative stress-sensitive miRNA; (6) Elucidate new functions of miRNAs in the development and progression of diseases under mechanical or oxidative stress (Fig. 3).

CONCLUSION

Deciphering how miRNAs regulate cardiovascular responses to mechanical and oxidative stress holds promise for improving CVD diagnosis, risk stratification, and targeted therapies.

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Compliance with Ethical Standards

Conflict of Interest Ziqi Shang and Kai Huang declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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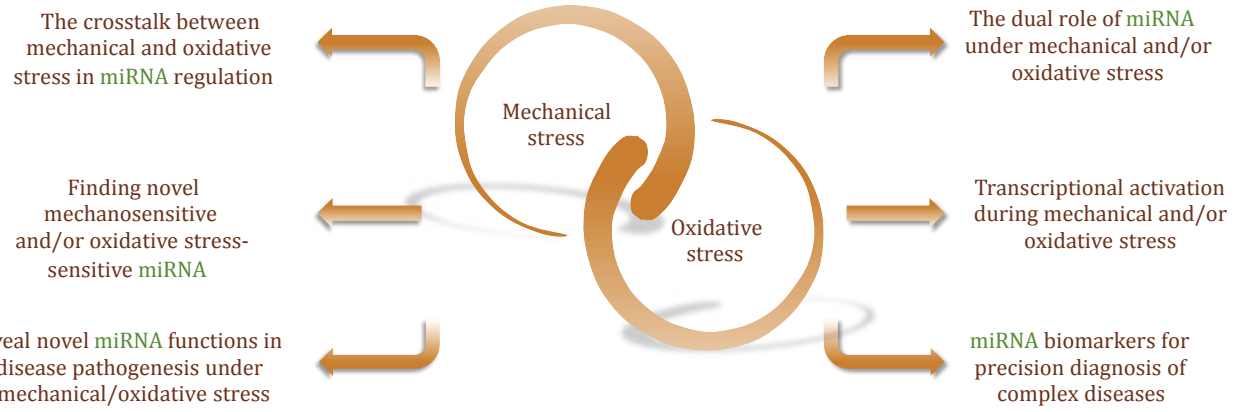

Fig. 3 New frontiers of miRNAs in mechanobiology and redox biology. Based on the current deficiencies in basic research and limitations in translational studies, research on miRNAs in vascular remodeling can be carried out from the above six aspects

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