Review (Narrative)

miRNA and Cardiac Hypertrophy

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SUMMARY

Cardiac hypertrophy is a frequent pathological reaction to hypertension, pulmonary hypertension, and other cardiovascular diseases. A typical feature of myocardial remodeling, cardiac hypertrophy can lead to heart failure and ultimately death. In recent years, studies have found some factors circulating within the blood of young mice can improve symptoms of heart hypertrophy in aged mice. GDF11 in the blood was once considered a key factor to extenuate cardiac hypertrophy, but subsequent studies question this conclusion. Recent genomic advances have revealed that non-coding RNA, including circular RNA, piRNAs, microRNAs and long non-coding RNAs, play an important role in gene expression and regulation, directly affecting pathophysiological mechanisms. The involvement of microRNAs within the myocardium and aortic valve in the regulation of pathophysiology may lead to the development of cardiovascular disease. Exosome-derived microRNA molecules in the heart are related to heart hypertrophy and failure. This article reviews the relevance of microRNAs to heart hypertrophy and the transported mechanism, which is helpful to discover new therapy and biomarkers for cardiac hypertrophy.■

KEYWORDS Cardiac Hypertrophy; Exosome; microRNA; Heart Failure

Sci Insigt. 2019; 28(1):17-24. doi:10.15354/si.19.re056

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HYPERTROPHY is a common reaction of cardiomyocytes to various forms of blood pressure overload, endocrine disorders, myocardial damage, and myocardial structure or contractile protein genetic mutation. Hypertrophy is a compensatory process whereby thickening of the ventricular wall maintains myocardial contractile function. However, in the case of persistent pathological stress, cardiac hypertrophy is accompanied by interstitial fibrosis, disruption of systolic function, and abnormalities in gene expression, energy metabolism, and electrophysiological characteristics that seriously impair the contractile and diastolic function of the heart, leading eventually to the development of abnormal heart rhythm, heart failure, or even sudden death. The treatment strategy for heart failure has undergone fundamental changes in the past 10 years, from focusing on short-term hemodynamic improvement to focusing on myocardial remodeling mechanisms, preventing and delaying the development of remodeling (1), and reducing heart failure mortality and hospitalization. Nonetheless, the 5-years mortality rate for heart failure is still similar to that for malignant tumors. One study found significant differences among three different hypertrophic model types: transverse aortic constriction, isoproterenol-induced hypertrophy and two genetic hypertrophy models that show mRNA characteristics (whether direct miRNA marks or main miRNA effects) are probably not dependable for prognosis (2). Thus, the mechanisms that define the process of pathology and lead to heart failure remain unclear, as does the role of non-coding RNAs in the development of heart disease.

BLOOD CIRCULATION FACTOR

In recent years, scientists have established parabiotic pairings between young and old mice, which shared circulatory system through recanalization of blood vessels, allowing cells and soluble factors to exchange rapidly and continuously between individuals sharing the circulation (3, 4). This technique can be used to explore factors affecting the function of tissues and organs in the circulatory system. Conboy (5) showed serum upregulated the Notch ligand from satellite cells of old mice, restored Notch activation in vitro. Environmental factors in young mice improve myocardial function in aged mice (3, 4, 6). Francesco (7) established a shared blood circulation in young (2 months) and old (23 months) mice, and observed decreased myocardial cell volume in aged mice after 4 weeks, and the presence of spleen GDF11 (7, 8) and the cardiac hypertrophy biomarker, atrial natriuretic peptide (ANF). The expression level of natriuretic protein (BNP) was significantly decreased, indicating that factors in the blood play a role in heart reconstruction and pathogenesis. Although the authors claim that GDF11 is effective for improving myocardial hypertrophy in the blood of young mice, their conclusions have been questioned by other scholars (9-12) since homology with GDF8 makes it hard to distinguish a protein effect specific to GDF11 (13). In addition, due to complex regulatory pathways and GDF11-specific post-translational forms, such as antagonists, the role of GDF11 in shared blood circulation on cardiac hypertrophy is unclear. Therefore, it is not clear which blood factors improved the symptoms of cardiac hypertrophy in old mice.

microRNAs AND CARDIAC HYPERTROPHY

microRNAs (miRNAs) are single-stranded noncoding RNAs of 19-24 nucleotides that are supplementary to the 3 non-coding region of the objective gene miRNA, and passively modulate gene expression by controlling mRNA translation and mRNA degradation (14). Evidence has shown that miRNA regulates cardiomyocyte growth (15), development, and angiogenesis in the cardiovascular system. In addition, miRNAs related to regulating heart hypertrophy are well-known (16). Little is understood about the miRNA factors related to upregulation that might prevent heart hypertrophy. MiRNAs are implicated in numerous cardiovascular diseases and can be targeted for therapeutic intervention, but their importance to regulating heart hypertrophy remains to probed (17). A systematic review of 72 studies and 52 different miRNAs, identified miR-1, miR-145, miR-133a/b, miR-208a/b, and miR-499(a) in serum and/or plasma as potentially identified in those with heart disease (18). Several studies demonstrate miR-1, miR-133a, miR-208a and others are related to the progress and development of cardiac hypertrophy.

miR-133a

To date, about 800 miRNAs have been found in the human heart. miR-133a, one of the most plentiful, has striated muscle tissue specificity. In humans, the miR-133 family, including miR-133a-1, miR-133a-2, and miR-

133b, found on chromosomes 18, 20, and 6, respectively, are important for regulating the functions of upstream genes and downstream transcription of target mRNA and translation of proteins, including RhoA, TGFβ/Smad, and PI3K/Akt (19), and normative pathways, for example the signaling concatenation of MAPK (20). Several animal models have shown that overexpression of miR-133 seems to guard against cardiac fibrosis and through the hypertrophy calcineurin-dependent signaling pathway and the JAK/STAT signaling pathway. Li (21) accumulated evidence showing that miR-133 is involved in heart cell growth, proliferation and survival, and the electrical conduction system in heart cells, which are vital to the development of heart hypertrophy as a response to heart fibrosis, and arrhythmia.

MiR-133a could prevent hypertrophy by preventing pathological remodeling to protect the heart. Research also found that miR-1 and miR-133 are specifically expressed in skeletal muscle, smooth muscle, and myocardium. One study found that miR-133 is important for preventing apoptosis; it binds to the apoptotic protein caspase9 in cardiomyocytes, which reduces its concentration in cells and inhibits apoptosis. MiR-133 can also bind indirectly to the apoptotic protein caspase3, inhibiting its function. Moreover, it is vital during the activity of cardiomyocyte proliferation and apoptosis. miR-133a could prevent hypertrophy by resistant pathological remodeling of the heart (22, 23, 24). MiR-133 function is a key factor for establishing a hypertrophy gene program. Carè identified three targets of miR-133 relevant to cardiac hypertrophy development: 1) RhoA regulates cardiac hypertrophy through a GDP-GTP exchange protein; 2) Cdc42 is implicated in cardiac hypertrophy through a signal transduction kinase; and 3) NELFA/Whsc2, a negative regulator of RNA polymerase II that is a nuclear factor associated with cardiogenesis. Both RhoA and Cdc42 are involved in cytoskeletal and myofibrillar rearrangements related to hypertrophy (25).

MiR-133 participates in the hypertrophy process of cardiomyocytes under the induction of high glucose in streptococci (STZ)-induced diabetes in the animal model; it not only participates in myocardial hypertrophy caused by abnormal genes, but also in myocardial hypertrophy of energy metabolism (26). Analysis of serum insulin levels in 200 diabetic patients, showed that glucose transporters play an important role in regulating glucose and participate in insulin-induced glucose uptake; overexpression of miR-133 in cardiomyocytes can cause insulin changes in the serum by specific pathways, that decrease the ability of glucose transporters to absorb glucose in cardiomyocytes, and change the process of cardiac hypertrophy (27). MiR-133b seems to have a vital role in regulating the hypertrophic gene program through upregulation of miR-133b to inhibit gene expression regulated by β-adrenergic receptor stimulation (28).The research shows a new and probably unique function for miR-133a, which regulates angiotensin type II in the paraventricular nucleus in rat models of congestive heart failure (29). DNA methylation reduces miR-133a expression, reactivating Cdc42 and RhoA and inhibiting cardiomyocyte hypertrophy (30). MiR-133a plays a role in mediating expression of MEF2A, MEF2C, SGK1 and GF1R, which lead to cardiomyocyte hypertrophy in diabetes (31).

miR-1

microRNA-1 (miR-1), a member of the muscle-specific microRNA family, has two separate loci, miR-1-1 and miR-1-2 controlled by an SRF promoter (32, 33). In the early stages of hypertrophy, decreased miR-1 regulates growth-related targets, such as cyclin-dependent kinase 9 (Cdk9) and Ras GTPase-activating protein (RasGAP) that higher expression is necessary for the development of cardiac hypertrophy (34). Huang et al. (35) showed that overexpression of miR-1 in stem cells can improve the migration of bone marrow mesenchymal stem cells (BMSCs). This can improve the survival rate of BMSCs and their ability to differentiate into cardiomyocytes, improving cardiac function and promoting myocardial tissue repair. The findings indicate that the miR-1 is directly and selectively targeting the mitochondrial calcium uniporter (MCU) axis, thereby upregulating the capacity of the mitochondrial Ca2+ machinery, which leads to cardiac hypertrophy. MiR-1 regulates the MCU content of cardiomyocytes in pathologic and physiologic hypertrophy.

miR-208a

miR-208a belongs to a miRNA family that includes miR-208b, and both of them are encoded by the α-cardiac muscle myosin heavy chain gene (Myh6) and β-cardiac muscle myosin heavy chain gene (Myh7), respectively. MiR-208a participates in cardiac electrical conduction and is found only in cardiomyocytes. Animal models have shown that miR-208 deletion has protective effects against heart hypertrophy, regulation of

the conduction system and myocyte apoptosis induced by doxorubicin, while over-expression of miR-208 in the mouse heart leads to heart rate malfunction and pathological heart hypertrophy (36). Montgomery silenced miR-208a with antisense oligonucleotides technology, and resulting in upregulation of Myh7, which improved cardiac function (37).

In the angiotensin II (Ang II)-induced hypertrophic model, miR-208a-3p promotes cell apoptosis-mediated regulation of autophagy, which hints at a possible treatment method for hypertrophic cardiac dysfunction (38). MiR-143-3p is inhibited in this model, which suppresses EKR5 and NF-κB pathway activation, and upregulates PPARδ expression. The results show that miR-143-3p plays a protective function in the progress of myocardial hypertrophy (39). Overexpression of miR-217 is detrimental to cardiac hypertrophy, fibrosis, and heart dysfunction through regulation of the target gene on chromosome ten (PTEN) (40).

Other miRNAs

Many studies suggest other important miRNA that may be biomarkers helpful for diagnosing heart failure. MiR-660-3p, miR-665, miR-1285-3p and miR-4491 show notable increases in heart and plasma when heart failure occurs. MiR-181a is one of the genes coding with the miR-17-92 gene cluster, located in the human genome in the third intron region of the primary transcript of the C130rf25 gene on chromosome 13, and located on chromosome 14 of the mouse genome. MiR-181a can regulate myocardial autophagy via the autophagy-related protein ATG5, thus mediating Ang II-induced myocardial hypertrophy (41). Wang discovered that a heart-related circular RNA (circRNA) is involved in isolating an endogenous miR-223 sponge and inhibiting miR-223 activity, resulting in the overexpression of ARC, the downstream target of miR-223, which indicates that miR-223 protects the heart from pathological hypertrophy (42). Negative regulation of MiR-206 affects the expression of FoxP1 in cardiomyocytes and increasing FoxP1 expression leads to weakened cardiac hypertrophy and survival (43). Zhang identified miR-29, which can prevent cardiac hypertrophy by targeting the nuclear peroxisome proliferator-activated receptor δ (PPARδ) and downregulating ANF (44). Cardiac hypertrophy leads to high expression of miR-132, and the cAMP-response element binding (CREB) transcription specifically inhibits miR-132 upregulation (45).

MiR-142-3p can alleviate cardiac hypertrophy by decreasing SH2B1 expression directly. It can also maintain mitochondrial function during cardiac hypertrophy (46). MiR-146a was identified as a SUMO1-targeting microRNA of the heart. High levels of miR-146a secreted from extracellular vesicles of the failing heart exert negative effects on the SUMO1/SERCA2a signaling axis, and hence on cardiomyocyte contractility (47). Research shows that upregulation of miR-330-3p aggravates cardiac hypertrophy induced by phenylephrine (PE) through the overexpression of X-inactive specific transcript (XIST) and S100B, which is one of EF-hand protein binding with calcium (48).

miR-217 as a direct target can be predicted and validated by PTEN, and its re-expression attenuated through miR-217-mediated cardiac hypertrophy and heart dysfunction (40). MiR-21 has distinct functions in different cardiac cell types，it is one of the most abundantly expressed and dysregulated miRNAs (49). MiR-21-3p binds to the 3' UTR of histone deacetylase-8 (HDAC8) and suppresses heart hypertrophy by increasing the expression of phospho-Akt and phospho-Gsk3β (50). Some studies suggest that overexpression of miR-21 is probably adverse during pathological heart remodeling (51). MiR-21 regulates the expression of matrix metalloprotease-2 through a phosphatase and tensing homologue pathway in the cardiac fibroblasts located in the infarct zone (52). However, other research indicates a positive effect of miR-21, with it playing an important function in regulation of cardiac myocyte apoptosis by aiming an antiapoptotic gene PDCD4 in an ischemia/reperfusion animal model (53). MiR-212 and 132 directly target the anti-hypertrophic gene, leading to overexpression of FoxO3 through hyperactivation of calcineurin/NFAT signaling, which leads to cardiac hypertrophy (54). MiR-199a impairs cardiomyocyte autophagy through complex signaling that includes glycogen synthase kinase 3β (GSK3β) and mammalian target of rapamycin (mTOR) in a transgenic mice model (55).

EXOSOMES AND miRNA

Paracrine plays an important role in improving heart function, which has been widely confirmed in research. The miRNAs in blood are mainly derived from exosomes, which are bioactive vesicles with a diameter of 30-200 nm and a lipid bilayer membrane structure that mediates cell-to-cell material interaction. exosomes

secreted by a variety of cells in the body and is widely found in various body fluids, for example blood, cerebrospinal fluid, urine, saliva, and ascites. Exosomes are rich sources of miRNAs compared to plasma, and the expression level of exogenous miRNA can reflect the physiology and pathology of secretory cells and functional status. Exosome-derived miRNAs molecules have better resistance to degradation and are more prominent as biomarkers. Valadi et al. (56) confirmed that exosomes secreted by hypertrophic cells transport miRNAs and mRNA translated proteins to the target cell simultaneously, and speculated that exosomes selectively transport RNA between cells, although the specific mechanism is not clear. More recent research (57) found miRNA in serum and plasma are mainly derived from exosomes and that exosomes can protect circulating miRNAs from RNase degradation. In addition, Arroyo et al. (58) believe that circulating miRNAs bind to Ago2 protein and construct a miRNA silencing complex that protects miRNAs and reduces their degradation from RNase (59).

The process of exosomes transporting miRNAs are as follows: 1) MiRNA is selectively encapsulated into a multivesicular cavity; 2) fusion of multivesicular and plasma membranes occurs and vesicles are secreted into extracellular space, leading to the formation of the exosome; 3) exosomes bind to the membrane of the target cell and fuse with the plasma membrane; 4) exosomes are endocytosed by target cells and then release their contents into the cells; 5) exosomes deliver miRNA to the cytoplasm of the target cell by the above two ways, and then specifically bind the 3' non-coding region of the target mRNA, thereby silencing target gene expression (59). Current research indicates that transporting miRNAs through exosomes regulates biosignal networks and participates in a variety of physiological processes. Therefore, research on miRNA has been a hot topic in the medical field in recent years, especially in stem cell therapy.

The expression level of miRNA changes with the development of disease, leading scholars to study miRNAs as potential biomarkers. Purification of exosomes from the supernatant of cell treated with Ang II reveals the overexpression of miR-217 in exosomes enhanced proliferation of fibroblasts in vitro (40). Exosomes from damaged myocardium contain high levels of miRNA-133a, which target and regulate the NFATc4 gene and protein, suggesting that inhibition of miRNA-133a can mitigate cardiac hypertrophy damage (60). Human exosomes that secrete nanovesicles coming from $CD34^+$ stem cells may regulate gene expression by entering cells and transferring miRNA precursors (61).

PROSPECTION

Exogenous miRNAs may become new indicators for disease diagnosis and provide new ways for targeted therapy, which will enable early diagnosis and treatment for certain diseases. This work provides new ideas and theoretical support for clinicians looking for new diagnostic markers. Although miRNA mechanisms are complex, future studies of exogenous miRNAs show promise in the following areas: i) Exploring moderately cost-effective and mature detection techniques to further clarify the types and biological characteristics of exosome-transported miRNAs in different disease; ii) Constructing a target gene-target miRNA-protein network to reveal the pathogenesis of disease from the gene to the protein level; iii) Exploring new technologies, such as transfecting miRNAs or miRNA antagonists into exosomes that can precisely regulate the expression of target proteins, as a new targeted treatment for disease.■

ARTICLE INFORMATION

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Author Contributions: Huo had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Gu & Liu.
Drafting of the manuscript: Gu
Critical revision of the manuscript for important intellectual content: All.

Statistical analysis: N/A.
Obtained funding: Liu.
Administrative, technical, or material support: Huo.
Study supervision: Huo.

Conflict of Interest Disclosures: The author declared no competing interests of this manuscript submitted for publication.

Acknowledgement: N/A.

Funding/Support: National Natural Science Foundation (81660690); Ningxia Natural Science Foundation (2018AAC03144); First-Class Discipline Construction Founded Project of NingXia Medical University and the School of Clinical Medicine (NXYLXK2017A05); Innovation and Entrepreneurship Project for Overseas Students in Ningxia Province..
Role of the Funder/Sponsor: N/A.

How to Cite This Paper: Gu J, Liu C, Wang Y, Huo Z. miRNA and cardiac hypertrophy. Sci Insigt. 2019; 28(1):17-24.

Digital Object Identifier (DOI): http://dx.doi.org/10.15354/si.19.re056.

Article Submission Information: Received, January 8, 2019; Revised: February 2, 2019; Accepted: February 4, 2019.■

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