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MicroRNAs, heart failure, and aging: potential interactions with skeletal muscle

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Abstract

MicroRNAs (miRNAs) are small noncoding RNAs that regulate gene expression by targeting mRNAs for degradation or translational repression. MiRNAs can be expressed tissue specifically and are altered in response to various physiological conditions. It has recently been shown that miRNAs are released into the circulation, potentially for the purpose of communicating with distant tissues. This manuscript discusses miRNA alterations in cardiac muscle and the circulation during heart failure, a prevalent and costly public health issue. A potential mechanism for how skeletal muscle maladaptations during heart failure could be mediated by myocardium-derived miRNAs released to the circulation is presented. An overview of miRNA alterations in skeletal muscle during the ubiquitous process of aging and perspectives on miRNA interactions during heart failure are also provided.

Keywords

MicroRNA; Heart failure; Exosomes; Skeletal muscle; Aging

Brief history

The original description of the first microRNA(miRNA) lin-4 was in studies seeking to better understand the genetic regulation of developmental timing in the nematode (*Caenorhabditis elegans*, or *C. elegans*) [67, 118]. These pioneering studies provided the first evidence that lin-14 expression was regulated by a posttranscriptional mechanism involving the interaction between the lin-14 3′-UTR and the small noncoding RNA lin-4. Almost a decade later, Pasquinelli et al. [85] reported the identification of let-7, a second miRNA from *C. elegans* that down-regulated lin-41 expression, and unlike lin-4, was expressed in a broad range of bilaterian animals including vertebrate, ascidian, hemichordate, mollusk, annelid, and arthropod. The revelation that let-7 was phylogenetically conserved in bilaterian animals

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was a major milestone in the history of the miRNA field because it suggested the posttranscriptional regulation of gene expression by miRNAs was more widespread than just *C. elegans*. Shortly thereafter, three independent reports described the identification of 30–50 new miRNAs in the human, fly, and worm, providing additional support for the idea that miRNAs may have an important role in the regulation of gene expression in animals [62, 65, 66]. The prescient nature of these early findings is revealed in the latest release of miRBase (version 21, June 2014; www.mirbase.org) which catalogs 35,828 mature miRNA sequences from 223 species with 2588 and 1915 human and mouse mature miRNAs, respectively.

Biogenesis

The vast majority of miRNAs are produced from RNA polymerase II transcription, resulting in a primary miRNA (pri-miRNA) transcript that has the characteristic 5′ m7G cap structure and 3′ poly(A) tail [12, 68]. Recent genomic mapping confirmed an earlier study showing that roughly half of annotated miRNAs are intragenic (exon, intron, 3′-UTR or 5′-UTR), located within protein-coding or noncoding RNA genes [44, 88]. In general, miRNA expression parallels the host gene, though new experimental evidence indicates that up ~35 % of intronic miRNAs are expressed as an independent transcription unit under regulation of its own promoter [82]. Once transcribed, the pri-miRNA forms a stem-loop structure that is recognized by the microprocessor complex which contains two core components, the RNase III endonuclease Drosha, and the double-stranded RNA-binding protein DGCR8 (DiGeorge Syndrome critical region gene 8) [47, 64]. DGCR8 binds to the stem-loop structure and then guides Drosha into position, cleaving ~11 base pairs (bp) from the base of the stem-loop to produce a 60–70 bp hairpin RNA molecule designated the precursor miRNA (pre-miRNA) [51].

Following pri-miRNA processing, the 60–70 bp precursor pre-miRNA is transported from the nucleus by Exportin 5, a nuclear export receptor, to the cytoplasm [10, 120]. Once in the cytoplasm, a second RNase III endonuclease, Dicer, cleaves the pre-miRNA to produce a ~22 nucleotide double-stranded RNA molecule in which one strand, known as the guide strand, is transferred to the RISC (RNA-induced silencing complex) containing Argonaute 2 (Ago2) and the RNA-binding protein Tarbp2 [TAR (HIV) RNA-binding protein 2]; the other strand is typically targeted for degradation [71]. The mature miRNA directs RISC to 3′-UTR of target mRNA through complementary binding of the miRNA seed sequence which results in inhibition of translation and/or degradation of the target transcript [84].

Tissue-specific expression

As quickly as miRNAs were shown to be conserved in different species, it was recognized that the expression of some miRNAs was restricted to certain tissues. One of the first examples of a tissue-specific miRNA was miR-1, which was found to be expressed exclusively in the human heart [62, 66]. The finding that some miRNAs were expressed in a tissue-specific fashion was confirmed in a study by Lagos-Quintana et al. [62], showing that miR-1, miR-122a, and miR-124a expression was restricted to striated muscle, liver, and brain, respectively. In an effort to identify new miRNAs, Sempere et al. [94] identified 30 miRNAs that were enriched or specifically expressed within a particular tissue [94]. These

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authors provided the first description of striated muscle-specific miR-1, miR-133a, and miR-206, which were later designated as myomiRs [75, 94].

The myomiR family has expanded since its original description to include miR-208a, miR-208b, miR-499, and, most recently, miR-486 [98, 107, 109]. Northern blot analyses showed that these new members of the myomiR family are strictly striated muscle specific (miR-208a, miR-208b and miR-499), being derived from the intron of different muscle-specific myosin heavy chain genes, or are highly enriched in muscle (miR-486) [98, 107]. Most myomiR family members are expressed in both the heart and skeletal muscle except for miR-208a, which is cardiac specific, and miR-206, which is skeletal muscle specific and enriched in slow-twitch muscles such as the soleus [77].

Circulating miRNAs

In the late 1960's, it became clear that substances from non-endocrine cells were released into circulation and affected the behavior of other cells in the body [30]. The discovery of these circulating proteins, termed "cytokines" in 1974 [17], opened up a new area of research related to how cells in different organ systems communicate with one another and affect whole-body homeostasis. It is now known that specific organs, such as skeletal muscle [34] and cardiac tissue [25], generate unique cytokines that are released into circulation under various conditions and have profound metabolic, mass regulation, and immunological effects on distant tissues. In 2007, Valadi et al. [104] discovered that miRNAs were released from mast cells and affected mast cells of differing origin. This discovery introduced a new non-hormone mechanism by which distant cells could influence one another at the molecular level. Moreover, similar to tissue-specific cytokines, tissue-specific miRNAs could potentially be released into circulation and exert distant effects [3].

The method by which miRNAs enter the circulation and are utilized by cells in other organ systems has not been thoroughly explored. It is known that ribonucleases are found in both plasma and serum [36], but extracellular miRNAs are stable and can be transmitted into and utilized by recipient cells [59, 81, 125]. Microvesicles, apoptotic bodies, non-vesicle-associated proteins (e.g., HDL), or RNA-binding proteins could mediate the transport process [3, 5, 24, 103, 111]. Valadi et al. [104] originally showed that miRNAs are packaged into exosomes in order to mediate intercellular communication. Arroyo et al. [5] then reported that the majority of circulating miRNAs are un-encapsulated and are chaperoned by protein complexes such as Argonaute 2, which maintains miRNA stability. In contrast to these findings [5, 103], Gallo et al. [41] showed that most miRNAs in human serum are within exosomes. Moreover, interference of the exosome biosynthesis process or disruption of exosomal membranes reduces extracellular miRNA content [59]. Most recently, it has been shown that serum miRNAs can be found in both vesicular and non-vesicular fractions in response to tissue damage in rats [95]. Although the manner in which miRNAs are transported in the circulation may be condition dependent, they appear to be abundantly expressed and likely exert effects in different tissue types.

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miRNAs, heart failure, and skeletal muscle

Heart failure is a general term for the heart's inability to pump sufficiently and maintain blood flow to meet the body's needs. The condition is characterized by a constellation of cardiac function criteria (further stratified by preserved ejection fraction or reduced ejection fraction) [57, 72] and could be caused by a variety of underlying mechanisms [53]. In general, though, significant cardiac ultrastructural, myofibrillar, biochemical, and molecular abnormalities underlie the pathophysiology of all forms of heart failure [26, 69]. Detrimental changes in skeletal muscle morphology and metabolism may also parallel the progression of heart failure [16, 70, 100, 113]. The heart is always metabolically active and is among the most vital organs. It is possible that heart tissue alterations associated with cardiac disease progression could affect skeletal muscle via myocardially derived miRNAs released into circulation.

Due to the varying etiology of heart failure, it would be difficult to ascribe a global miRNA signature that characterizes all human cardiac dysfunction. However, a number of misregulated miRNAs are recurrent in the heart failure literature [79] and confirmed to be altered in various forms of diseased and damaged human cardiac tissue. Namely, miR-1 [11, 14, 63, 74, 83, 102, 119], miR-21 [56, 63, 74, 102, 108, 112, 119], miR-24 [55, 74, 108], miR-29b [63, 110], miR-133a and b [11, 14, 21, 29, 74, 91, 99, 108], miR-199 [55, 63, 108], miR-208 [11, 90], miR-214 [55, 83, 108], and miR-499 [55, 73, 74] are consistently affected in human heart failure of varying origin and degree. This panel of miRNAs may serve as a preliminary template for miRNA-mediated heart–skeletal muscle communication during heart failure.

Many of the aforementioned miRNAs present in diseased myocardium are also enriched in the circulation following acute cardiovascular trauma. For instance, circulating miR-1, miR-21, miR-29a, miR-133a, miR-208a and b, and miR-499 are elevated after acute myocardial infarction (MI) [1, 18, 19, 31, 61, 115, 117, 127]. MiRNA appearance in the circulation may simply be a consequence of large-scale cardiac membrane disturbance and subsequent release. However, miRNAs that are up regulated in heart tissue also manifest in the circulation during less traumatic chronic cardiovascular conditions. MiR-1 and miR-133a are elevated in the circulation with unstable angina, cardiomyopathy [61] and coronary atherosclerosis [9, 35]; miR-208a tends to be elevated with stable coronary artery disease [35]; miR-21 and miR-29 are up regulated with ventricular fibrosis [89, 112] and hypertrophic cardiomyopathy [89]; miR-499 and miR-208b are increased with viral myocarditis [18]; and miR-21 is up regulated with various degrees of diagnosed heart failure [13, 46, 101] as well as coronary artery disease [50]. Most recently, a panel of circulating miRNAs sensitive enough to distinguish between chronic heart failure with preserved versus reduced ejection fraction was identified, and circulating miR-221 and miR-328 levels increased the discriminatory power of circulating B-type natriuretic peptide for assessing heart failure [116]. Thus, circulating miRNAs can serve as biomarkers for both acute myocardial trauma as well as chronic heart conditions.

Direct release of miRNAs from the human heart is evident under various circumstances [23, 45]. Furthermore, myocardial and circulating miR-21 levels correspond in aortic stenosis

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patients [112], miR-208a (a cardiac-specific miRNA) is enriched in serum-derived exosomes [8], and the relative abundance of circulating cardiac-specific miRNAs reflects the ratio found in heart tissue [2]. Cardiomyocytes in culture are shown to release extracellular vesicles [43, 49, 114] that contain miRNAs [42]. The content and quantity of exosomes are also responsive to external stimuli [42, 43]. More work is needed to describe the miRNA profile of human cardiomyocyte-derived extracellular vesicles, but consistent with what is found in myocardial tissue and the circulation with heart failure, cardiomyocytes cultured from human progenitor cells robustly express miR-1 and miR-499 [97]. In vitro experiments also show that cardiac fibroblasts secrete miR-enriched exosomes that affect cardiomyocyte gene expression and hypertrophy [6]. Cardiomyocyte-derived exosomes also facilitate communication with endothelial cells [42]. Various lines of evidence strongly indicate that cardiac tissue can synthesize and release miRNA-containing vesicles that change in response to stimuli and could affect gene expression in distant tissues. It is conceivable that sustained miRNA release from the heart during heart failure could facilitate communication with skeletal muscle.

Similar to what occurs between cardiac fibroblasts, endothelial cells, and cardiomyocytes, myoblasts and myotubes are shown to communicate with each other through exosome-derived miRNAs in vitro [37, 38]. It is therefore likely that mature skeletal muscle regulates its microenvironment via exosomes/miRNAs in vivo and that miRNAs from distant tissues (namely myocardium) could affect skeletal muscle molecular events. Of the miRNAs enriched in both cardiac muscle and the circulation during heart failure, myomiRs (namely miR-1, miR-133, miR-208, and miR-499 [78, 106, 107]) are shown to strongly affect developed skeletal muscle. Of these myomiRs, miR-1 and miR-133a are elevated in the circulation with various forms of cardiovascular disease [61] and remain elevated for 3 months post-MI [127]. It was also recently reported that circulating myomiRs (including miR-1) are elevated in the most advanced heart failure patients [2]. Suppressed miR-1 and miR-133a are implicated in mature skeletal muscle hypertrophy [77], likely through anti-repressive targeting of the IGF-1 growth signaling axis [32, 54]. Thus, increased circulating miR-1 and miR-133a could facilitate skeletal muscle atrophy in the wake of a traumatic cardiovascular event (Fig. 1). Interestingly, once heart failure is compensated with a left ventricular assist device, myomiR levels in the myocardium (specifically miR-1, miR-133a, and miR-133b) are decreased [91]. More work is needed to elucidate how different cardiac conditions affect specific myomiRs in the circulation.

Heart–skeletal muscle communication via miRNAs during heart failure is speculative at this point, but it is not without precedent. Other compounds such as myostatin released from cardiac tissue during heart failure can strongly regulate skeletal muscle mass [52]. Emerging evidence suggests that diseased cardiac tissue is a major source of circulating miRNAs [9] and that miRNAs (via extracellular vesicles or some other mechanism) participate in intercellular communication [3]. Further research on how miRNAs are released from cardiac tissue, under what conditions they are released, how skeletal muscle is potentially targeted by extracellular vesicles/miRNAs, and the specific effects of these miRNAs in skeletal muscle is warranted. The miRNA expression profile of skeletal muscle in heart failure patients should also be evaluated. Finally, elucidating the role of non-myomiR miRNAs, such as heart failure- [13] and skeletal muscle fibrosis-associated miR-21 [4, 60, 101], is

necessary to fully understand how circulating miRNAs can contribute to diseased conditions in various tissues.

miRNAs and the interaction between aging, heart failure, and skeletal muscle

Among the most pronounced and noticeable changes that occur with aging is an inevitable loss of skeletal muscle mass and subsequent function [15]. This condition, termed sarcopenia, is caused by a complex interplay of factors and is compounded by attenuated responsiveness to hypertrophic stimuli [86, 96]. Skeletal muscle is the largest organ in the body and synthesizes numerous miRNAs, including skeletal muscle-specific myomiRs that are responsive to external stimuli [75–78]. MicroRNA abundance, specificity, and plasticity suggest these molecules are important for skeletal muscle regulation.

In healthy older individuals, basal levels of intramuscular myomiRs and cellular proliferation-related miRNAs differ compared to younger individuals, which could conceivably contribute to age-associated atrophy [27, 28, 87]. Interestingly, basal miR-1 is lower in muscle of young physically active (~27 year) and lifelong-exercised older men (~70 year) versus inactive older men [122], indicating fitness level may influence baseline miRNA expression. However, following acute resistance exercise with amino acid ingestion in untrained individuals, miR-1 is reduced in young but not old skeletal muscle [27]. Similarly, age-associated alterations to miR-1 and miRNA-mediated IGF-1 signaling [87, 121] as well as attenuated global miRNA responsiveness to exercise in skeletal muscle [87] have been reported. No statistical difference in skeletal muscle or circulating myomiRs (miR-1, miR-133a, miR-206, miR-208b, and miR-499) after resistance training in older individuals (65–80 year) further suggests age-associated miRNA inflexibility at multiple anatomical levels [22, 124]. Blunted miRNA plasticity in response to exercise dovetails with attenuated skeletal muscle global gene expression seen with exercise training as age progresses [86]. The coexistence of reduced miRNA and mRNA expression with aging could be partly attributable to the fact that 35 % of mammalian miRNA are located within annotated genes [48] and are transcribed in parallel with their host transcripts [88].

In addition to miRNA misregulation with aging in skeletal muscle, basal cardiac miRNA expression appears to be altered with age-related heart dysfunction [92, 126]. It is challenging to tease apart the effects of aging and heart failure as aging is a risk factor for the development of cardiac dysfunction [20]. However, recent circulating miRNA findings provide some insight into the individual effects of these conditions. A distinct circulating miRNA signature characterizes the aging process [123], but circulating miRNAs profiles are unique between aged individuals with or without heart failure [93]. Interestingly, circulating miR-1 appears to be *reduced* as the severity of heart failure increases in elderly individuals (>68 year) [101]. Thus, an interaction between aging and aging with heart failure appears to manifest in the expression of circulating miRNAs.

The relationship between aging, heart failure, and skeletal muscle is largely unknown. However, age-related heart failure is characterized by alterations to microRNAs associated with fibrotic deposition and extracellular matrix accumulation in cardiac tissue [105].

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Excessive fibrosis in any tissue is generally associated with reduced performance and negative health outcomes. In skeletal muscle, stem cells (satellite cells) regulate fibrotic deposition in some paracrine fashion [39], and a lack of satellite cells exacerbates fibrosis with aging [40]. Since cardiac tissue possesses stem cells [7, 80], it is possible that these cells regulate fibrosis similar to skeletal muscle via secreted miRNAs [58] and are negatively affected by heart failure and aging. These fibrosis-related miRNAs in circulation may conceivably influence skeletal muscle extracellular matrix remodeling as well. To this point, patients with diagnosed myocardial fibrosis resulting from hypertrophic cardiomyopathy have altered levels of circulating miRNAs implicated in fibrotic deposition [33]. Determining what tissues (e.g., skeletal muscle, cardiac) and cell types are releasing miRNAs into circulation and how these miRNAs affect other tissues is an important next step in defining the role of miRNAs in senescence and heart failure.

Conclusion

MiRNA biology is a burgeoning area of research since these small noncoding RNAs are known to elicit a powerful effect in a variety of cell types. Both heart failure and aging are characterized by distinct miRNA profiles in striated muscle as well as the circulation. myomiRs, or muscle-specific miRNAs, are noticeably affected with heart failure and aging and could mediate inter-organ communication through packaging and release into the circulation. Exercise appears to have an effect on miRNA expression during heart failure and aging, but more research on how miRNAs (both tissue- and non-tissue-specific) are altered during different physiological processes, their target mRNAs, and how they are packaged, released into circulation, and taken up and utilized by distant cells is warranted.

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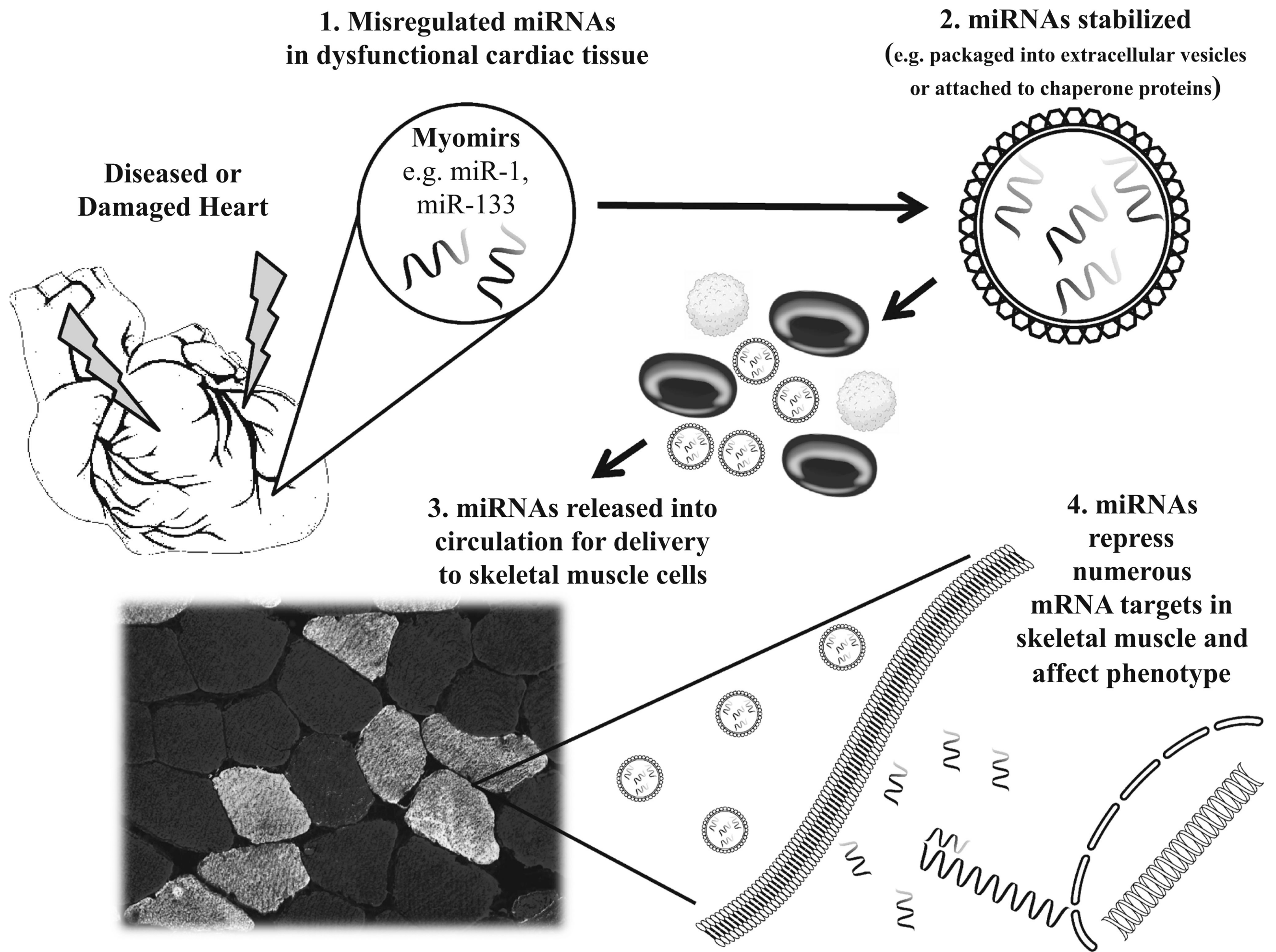

Fig. 1.

Theoretical mechanism by which myocardially derived miRNAs expressed during cardiac dysfunction and/or trauma may communicate with skeletal muscle to regulate mass and function