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Impact of miRNAs on cardiovascular aging

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Abstract

Aging is a multidimensional process that leads to an increased risk of developing severe diseases, such as cancer and cardiovascular, neurodegenerative, and immunological diseases. Recently, small non-coding RNAs known as microRNAs (miRNAs) have been shown to regulate gene expression, which contributes to many physiological and pathophysiological processes in humans. Increasing evidence suggests that changes in miRNA expression profiles contribute to cellular senescence, aging and aging-related diseases. However, only a few miRNAs whose functions have been elucidated have been associated with aging and/or aging-related diseases. This article reviews the currently available findings regarding the roles of aging-related miRNAs, with a focus on cardiac and cardiovascular aging.

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1 Introduction

Aging is a multi-factorial process characterized by a progressive loss of physiological integrity and the remodeling of various molecular pathways involved in cellular and tissue homeostasis; this process increases disease susceptibility and mortality and leads to the functional decline of tissues and organs.[1–3] The relevance of aging-related diseases, including cancer, cardiovascular disease, diabetes, osteoporosis, and various neurodegenerative diseases, should be considered not only because they are the leading causes of mortality but also because of the high frequency of these diseases and the potential for decreased quality of life.[4] Several studies have shown that the onset of these aging-associated disorders is associated with alterations in microRNAs (miRNAs, miRs), which suggests that miRNAs are novel cellular senescence regulators.[5–9] miRNAs are small non-coding RNAs that are approximately 18–25 nucleotides long, and they regulate gene expression at the post-transcriptional level via target mRNA degradation and/or translational suppression via binding to the 3'-untranslated region (3'-UTR).[10] As negative regulators of gene regulation, miRNAs are involved in essential physiological and pathophysiological processes, including development, homeostasis, differentiation, proliferation, apoptosis, and various diseases.[9,11] Because of the multiple biological functions of miRNAs, it is not surprising that miRNAs are also involved in cellular and organismal aging and age-related diseases.[12,13] Recent evidence has suggested that the expression profiles of miRNAs are dysregulated during cellular senescence and aging both *in vitro* and *in vivo*,[14–16] and some miRNAs target conserved pathways of aging, such as the insulin/insulin-like growth factor (IGF) pathway, the target of rapamycin (TOR) pathway, and pathways regulated by the sirtuin family; these pathways are all associated with cardiovascular diseases and neurodegenerative diseases.[13,17] However, the tissue-specific significance of such age-dependent alterations of miRNAs, especially in the cardiovascular system, has not been fully elucidated yet. At the cellular level, aging changes the phenotypic and functional characteristics of cells involved in the cardiovascular system, including cardiomyocytes, cardiac fibroblasts, vascular smooth muscle cells, and endothelial cells, and these alterations collectively contribute to age-dependent alterations of the heart and vasculature.[18] Therefore, cardiovascular aging can be defined as aging-associat-

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ed alterations of the cardiovascular system (i.e., decreased heart rate, increased arrhythmia, hypertrophy, fibrosis, and arterial stiffness) due to age-dependent changes of individual component cells. In this review, we summarize previously reported evidence that potentially links age-dependent miRNA changes to cardiovascular aging.

2 miRNAs and cardiac aging

Currently, little is known about the roles of miRNAs in cardiac aging. Although the expression levels of miRNAs are altered in aged hearts, few miRNAs whose functions mediate the aging process in the heart have been identified (Table 1).[9,19] The following are examples of these miRNAs.

2.1 miR-34a

The entire miR-34 family is composed of three members: miR-34a, miR-34b, and miR-34c.[20] miR-34a is speculated to serve as a tumor suppressor because miR-34a expression is commonly down-regulated in human cancers.[20,21] miR-34a regulates the expression of target proteins involved in cancer formation, metastasis, and cell viability. The identified mRNA targets of miR-34a include mRNAs involved in cell cycle progression (G1/S transition), anti-apoptotic proteins, and invasion.[22–24] In addition to having anti-cancer potential, miR-34a has been suggested to be a risk factor in cardiac aging.[25,26] Boon, *et al.*[27] demonstrated that the hearts of old mice (18–20 months of age) exhibited increased cardiomyocyte death, developed hypertrophy and fibrosis, and had shortened telomeres. Interestingly, the miR-34a expression was significantly increased in aged hearts. This previous study showed that the inhibition of miR-34a by antisense oligonucleotides (antagomir; ant-34a) reduced cardiomyocyte apoptosis both *in vitro* and *in vivo*, whereas the overexpression of miR-34a by pre-miR-34a accelerated cell death. The authors generated miR-34a knockout (miR-34a$^{-/-}$) mice, and these mice showed less age-related deterioration of cardiac contractile function and less cardiac hypertrophy and apoptosis. Moreover, cardiac miR-34a is up-regulated in mice with a genetic deletion of Ku80 (an animal model of accelerated aging) and in mice with acute myocardial infarction (AMI), and the decrease in miR-34a induced by locked nucleic acid (LNA)-based anti-miRs reduced the worsening of cardiac dysfunction. The authors identified phosphatase 1 nuclear targeting subunit (PNUTS) as a novel target of miR-34a using three miRNA target prediction tools (miRanda, PicTar, and Targetscan 5.1) and the mRNA expression profiles in aged and young mice. PNUTS is down-regulated in aged hearts, and it interacts with the telomeric repeat binding factor 2 (TRF2). Overexpression of PNUTS prevented the cardiomyocyte apoptosis induced by H_2O_2, inhibited the shortening of the telomere length, and decreased the cardiac contractile impairment *in vivo*. These results indicate that the inhibition of miR-34a may represent an effective therapeutic strategy for preventing cardiac aging and restoring cardiac contractile function after myocardial infarction.

2.2 miR-22

Jazbutyte and colleagues demonstrated that miR-22 is highly up-regulated during cardiac aging in mice.[28] The expression of miR-22 differs in various cardiac cell types, including cardiomyocytes, smooth muscle cells, cardiac fibroblasts, and endothelial cells. MiR-22 is enriched in cardiac fibroblasts and smooth muscle cells, whereas its expression is relatively low in both cardiomyocytes and

Table 1. miRNAs implicated in cardiac and vascular aging.

miRNA	Targets	Functions	References
Cardiac aging			
miR-34a	PNUTS	Promotes age-related and MI-induced cardiomyocyte cell death and cardiac dysfunction	[24–26]
miR-22	Mimecan	Increases senescence and cardiac fibroblast activity	[27]
miR-18/19	CTGF TSP-1	Inhibits cardiac fibrotic remodeling	[30]
miR-17-3p	PAR-4	Attenuates cardiac aging and fibroblast cellular senescence	[39]
Vascular Aging			
miR-34a	SIRT1	Induces endothelial senescence and inflammation, as well as arterial dysfunctions	[50,51]
miR-22	AKT3	Induces senescence and decreases EPC proliferation and migration	[52,55]
miR-29	ECM proteins	Induces aortic dilation and aneurysms	[56–59]
miR-125a-5p	RTEF-1	Induces EC dysfunctions (down-regulates angiogenic growth factors)	[61]
miR-146a	NOX4	Inhibits EC senescence	[62]
miR-217	SIRT1	Increases eNOS expression and promotes EC senescence and dysfunction	[64]

EC: endothelial cells; EPC: endothelial progenitor cells; eNOS: epithelial nitric oxide synthase; MI: myocardial infarction.

endothelial cells. One of the direct targets of miR-22 is the proteoglycan mimecan (also termed osteoglycin), which plays important roles in modulating the cell cycle and the structure of the extracellular matrix (ECM),[29] and mimecan is down-regulated in the aging heart. A negative correlation between miR-22 and mimecan expression is present in cardiac fibroblasts, and mimecan has been associated with the regulation of senescence and migratory activity of cardiac fibroblasts. Although the underlying mechanisms of how the miR-22-mediated down-regulation of mimecan improves cardiac function in aging hearts remain unclear, the up-regulation of miR-22 and the subsequent down-regulation of mimecan exacerbate cardiac aging via an increase in senescence and cardiac fibroblast activity.[28]

2.3 miR-18 and miR-19

The miR-17-92 cluster consists of the following six mature miRNAs: miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92a.[30] The roles of miR-17-92 in age-related cardiac remodeling and heart failure, including arrhythmias, have not been clearly elucidated compared with their roles in tumorigenesis.[31] The miR-17-92 cluster is activated by c-Myc, has been linked to cancer pathogenesis and is thought to be pro-tumorigenic.[32] Studies have shown that the expression levels of miR-18a and miR-19a/b, which are members of the miR-17-92 cluster, are lower in failure-prone hearts, and this change increases the targeting of two matricellular proteins: connective tissue growth factor (CTGF) and thrombospondin-1 (TSP-1).[32,33] Furthermore, when overexpressed in mice, miR-18 and miR-19a/b repressed the expression of CTGF and TSP-1, which regulate fibrotic remodeling and size, and this repression eventually led to aging-related cardiac remodeling.[34]

2.4 miR-17-3p

As previously discussed, miR-17-92 cluster members play important roles in cell cycle, proliferation, and apoptosis.[35] The miR-17-92 cluster has been extensively studied as a polycistronic onco-miR;[36,37] however, accumulating evidence indicates that the miR-17-92 cluster is also a novel regulator of cardiac damage, development, and diseases.[30,35,38,39] Recently, Du *et al*.[40] reported that miR-17, a member of the miR-17-92 cluster, is related to cardiac senescence and that miR-17-3p diminishes cardiac aging in mice. Prostate apoptosis response 4 (PAR-4; also referred to as PAWR) is a tumor suppressor protein and selectively induces cell death in cancer cells.[41] PAR-4 is the direct target of miR-17-3p and is a negative regulator of CCAAT/enhancer-binding protein B (CEBPB), which binds to the CEBPB promoter region and represses CEBPB transcription.[40] The decreased PAR-4 expression via miR-17-3p leads to increased transcriptional activity of CEBPB and FAK (focal adhesion kinase), which attenuates mouse cardiac aging and cardiac fibroblast cellular senescence.

3 miRNAs and vascular aging

Compared to cardiovascular aging, vascular aging is a more specific term that refers to age-dependent changes of vasculature, including atherosclerotic plaque, arterial stiffness, dilation, fibrosis, increased intimal thickening, and endothelial dysfunction.[42] Vascular aging is tightly linked to alterations in the biomechanical and structural properties of the vascular wall, including endothelial and smooth muscle cell dysfunctions or apoptosis, as well as increased arterial stiffness (Table 1).[43–45]

3.1 miR-34a

Sirtuin 1 (SIRT1) regulates the cell cycle, cellular senescence, and metabolism.[46–48] In human fibroblasts, increased expression of SIRT1 can delay cellular senescence and extend the cellular life span.[49,50] Aged endothelial cells express high levels of miR-34a and low levels of SIRT1 protein. The overexpression of miR-34a decreases the SIRT1 protein level and increases the acetylated p53 level in endothelial cells.[23,51] Badi, *et al*.[52] reported that miR-34a regulates vascular smooth muscle cell senescence and inflammation, in part, via the down-regulation of SIRT1 while increasing senescence-associated secretory phenotype factors.

3.2 miR-22

AKT3 is a target of miR-22, the expression of which is reportedly up-regulated in aged endothelial progenitor cells (EPCs).[53] AKT regulates the signaling of multiple biological and pathophysiological processes.[54,55] The overexpression of miR-22 in young EPCs induces cell senescence and decreases proliferation and migration via the down-regulation of AKT3 expression.[56]

3.3 miR-29

Aging is closely related to aortic dilation and aneurysm formation. Using miRNA microarrays, bioinformatics tools (Sylamer and MirExTra), and real-time PCR, Boon and colleagues demonstrated that the expression levels of the miR-29 family (miR-29a, miR-29b, and miR-29c) are increased in the aortic tissue from old mice compared with young mice.[57] Interestingly, the abnormal expression of ECM proteins is associated with aortic aneurysm formation and is regulated by the miR-29 family.[58–60] The expression

of miR-29 family members is increased in two animal models, angiotensin II-treated aged mice (an aortic dilation model) and Ribulin-$4^{R/R}$ knockdown mice (a genetically induced aneurysm model), as well as in biopsies from human thoracic aneurysms. In addition, the down-regulation of miR-29 via an LNA-modified antisense oligonucleotide restored ECM protein expression and attenuated the angiotensin II-induced dilation of the aorta *in vivo*. Thus, the strategy of restoring the expression of ECM proteins via the down-regulation of miR-29 family members may provide a new therapeutic technique for treating vascular aging-related diseases, including aortic dilation and aneurysm formation.

3.4 miR-125a-5p

The expression levels of endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), and other cytokines are decreased in aged endothelial cells (ECs), which are linked to impaired endothelial dysfunction.[61] Che, *et al.*[62] performed microarray analysis to identify the changes in the miRNA expression between young and aged mouse arterial ECs. The microarray results demonstrated that miR-125a-5p is significantly increased in aged ECs compared with young ECs. miR-125a-5p is associated with angiogenesis; the overexpression of miR-125a-5p in young ECs decreases angiogenic tube formation and the eNOS and VEGF expression, whereas the inhibition of miR-125-5p in old ECs via anti-miR-125a-5p restores angiogenic function and up-regulates angiogenic growth factor expression. These biological activities of miR-125a-5p are related to related transcriptional enhancer factor-1 (RTEF-1), a member of the transcriptional enhancer factor (TEF) family. Therefore, an increase in miR-125a-5p expression induces EC dysfunction via the suppression of both angiogenic growth factors, such as eNOS and VEGF, and RTEF-1 in aging ECs.

3.5 miR-146a

During the aging of human umbilical vein endothelial cells (HUVECs), miR-146a is down-regulated.[63] A potential molecular target of miR-146a is NOX4, which is a member of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family and generates reactive oxygen species (ROS).[64] The aging-related down-regulation of miR-146a in human ECs induces NOX4 overexpression and EC senescence.

3.6 miR-217

In contrast to the trend for miR-146a, the expression level of miR-217 progressively increases during the aging of HUVECs and human aortic endothelial cells.[65] SIRT1 is a putative target of miR-217, and the loss of SIRT1 function has been connected to endothelial dysfunction and premature senescence.[66] The regulatory mechanism underlying the angiogenic activity of ECs via SIRT1 involves decreased Forkhead box protein O1 (FoxO1) expression and eNOS acetylation, as well as increased eNOS expression.[65,67,68] Thus, miR-217-mediated SIRT1 suppression promotes EC senescence and dysfunction.

4 Conclusions

Aging is a high risk factor for cardiovascular diseases and is associated with a poor quality of life and an increased burden on society and families. Therefore, aging societies have a strong desire to develop effective anti-aging strategies. Accumulating evidence suggests that miRNAs are deeply involved in cardiac and cardiovascular aging. The alteration of miRNA expression levels during aging can exacerbate or attenuate cardiac and/or cardiovascular dysfunction and senescence. Although the importance of miRNAs in aging-related heart and cardiovascular diseases is commonly acknowledged, the underlying cellular and molecular mechanisms must be further elucidated. Functional investigation of miRNAs as novel therapeutic targets of aging-associated diseases will facilitate the development of novel therapies and improve the quality of life in aging individuals.

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