14 Non-coding RNAs and Cardiac Aging

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Abstract

Aging is an important risk factor for cardiovascular diseases. Aging increasing the morbidity and mortality in cardiovascular disease patients. With the society is aging rapidly in the world, medical burden of aging-related cardiovascular diseases increasing drastically. Hence, it is urgent to explore the underlying mechanism and treatment of cardiac aging. Noncoding RNAs (ncRNAs, including microRNAs, long noncoding RNAs and circular RNAs) have been reported to be involved in many pathological processes, including cell proliferation, cell death differentiation, hypertrophy and aging in wide variety of cells and tissues. In this chapter, we will summarize the physiology and molecular mechanisms of cardiac aging. Then, the recent research advances of ncRNAs in cardiac aging will be provided. The lessons learned from ncRNAs and cardiac aging studies would bring new insights into the regulatory mechanisms ncRNAs as well as treatment of aging-related cardiovascular diseases.

Keywords

Cardiac ageing · miRNA · Long noncoding RNA · Circular RNA

1 Introduction

Aging is a main factor for cardiovascular diseases. It has been reported that the incidence of myocardial infarction, cardiac hypertrophy, atrial fibrillation and coronary arteriosclerosis were dramatically increased with aging [1–3]. Besides, myocardial structure and function changed with ageing always accompanied with pathological conditions, such as aortic stiffening, atrial enlargement, loss of myocytes, pathological hypertrophy and proliferation of cardiac fibroblasts [4]. Additionally, aged heart making it more sensitive to cardiovascular risk factors [5, 6]. Therefore, exploring the molecular mechanism of cardiac aging is helpful to prevent cardiovascular risk and reveal the occurrence of cardiovascular diseases.

Along with transcriptomics, next generation sequencing and bioinformatics development, the concept that proteins were the main regulators in

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gene expression regulation has been updated in the past two decades. Only 2% of the transcribed genomic DNA can be translated into protein, mostly of the transcripts can't translatable, which were known as noncoding RNAs (ncRNAs). NcRNAs have been shown to be involved in almost all physiological and pathological processes of heart. In this chapter, we will summarize (1) the physiology and molecular mechanisms of cardiac aging, (2) the function of ncRNAs in cardiac aging.

2 Cardiac Ageing

Cardiac aging is a heterogeneous process which is characterized by damaged genomic DNA, shortened telomere length, altered epigenetic modifications, as well as accumulated senescent cells [7].With the growth of age, the performance of the heart gradually decline, thus, the structural and functional capacity of the heart would be impaired, which is the mainly inducing factor of cardiovascular disease in elderly. Cardiovascular disease is the major reason of death in the western world. Recent statistical study has reported a 171% increase in cardiovascular deaths among patients ages 65–85 [8]. The physiological changes of cardiac aging mainly include left ventricular hypertrophy, diastolic dysfunction, valve degeneration, increased cardiac fibrosis, increased prevalence of atrial fibrillation, and decreased maximum exercise ability [9]. Although the phenotype of heart aging can be well characterized, the study on the molecular mechanism of heart aging is just beginning. Here, we mainly focus on the physiological change and molecular mechanism of cardiac aging in view of the recent research progress, and provide new treatment opportunities for age-related cardiovascular diseases.

2.1 Physiology of Cardiac Aging

2.1.1 Ventricular Changes

Increased left ventricular thickness is an important factor for cardiovascular disease. According to the Framingham Heart Study and the Baltimore Longitudinal Study of aging, left ventricular wall thickness significantly increased with age in both men and women regardless of whether they previously had hypertension. Caused by decreased ventricular elasticity, fibrosis and delayed ventricular active diastole, left ventricular filling in early diastole may gradually weaken in elderly. Moreover, the decreased rate of calcium ATPase calcium reuptake in myocardial reticulum will further aggravate this damage. As a result, in order to maintain the filling of left ventricle with increase of age, atrial contraction gradually increases, leading to increased atrial pressure, which is not benefit to hypertrophy and increases the incidence of atrial fibrillation [1, 2, 10]. Studies have shown that, the ratio of early (E) and late (A) diastolic left ventricular filling decreased in elderly people [11, 12], which is clinically defined as cardiac diastolic dysfunction [13] In addition, cardiac aging also leads to a decrease in maximal heart rate and induces a range of cardiovascular diseases [14, 15].

2.1.2 Valvular Changes

Echocardiography revealed that 30–80% of the elderly had aortic valve sclerosis [16–18], mainly including aortic lobular calcification and aortic ring [19, 20]. Valve sclerosis are age-related valve lesions which include myxomatosis degeneration and collagen deposition. Elderly patients with cardiac hypertrophy, hyperlipidemia, hypertension, end-stage renal disease, and congenital bicuspid aortic valve have an increased risk of cardiovascular disease and mortality compared with their peers [21–24].

The prevalence of aortic stenosis increased with age. Fibrosis and valve calcification can lead to aortic stenosis [21]. In order to maintain adequate systolic function, left ventricular wall thickening enables effective pumping of blood, while excessive left ventricular wall thickening causes left ventricular dilatation, result in systolic function. In addition, with age, aortic valve insufficiency, blood flows from the aorta to the left ventricle, resulting in increased left ventricular volume, accounting for 13–16% of the elderly with aortic regurgitation [17].

Mitral annular calcification (MAC) is a degenerative disease involving the mitral annulus. MAC patients often suffer from a complications, such as hypertension, aortic stenosis, mitral valve prolapse, heart failure, atrial fibrillation, and so on [25, 26]. Besides, mitral regurgitation is another common abnormality in the elderly. Mitral regurgitation happens when the mitral valve does not seal tightly, causing blood to flow back to the heart, resulting in insufficient blood flow. Two major causes of mitral regurgitation are myxomatous degeneration and ischemic heart disease [27]. Changes in central ventricles and valves during cardiac aging result in cardiac functional impaired and more likely to development into heart failure [14]. Which makes the elderly heart more sensitive to risk factors, leading to cardiovascular mortality in the elderly population.

2.2 Molecular Mechanisms of Cardiac Aging

2.2.1 Nutrition and Growth Signaling

There are many cell signaling regulators involved in the process of heart failure, many of which are associated with cardiac hypertrophy. Insulin-like growth factor-1 (IGF-1) is an important signaling pathway participate in this process [30, 31], Normally, depression of IGF-1 level can lead to heart failure, which may be reduced if drugs are used to increase IGF-1 levels in the body [32–34]. At the same time, IGF-1 can weaken the oxidative stress response in the organ, making it less sensitive [28]. Therefore, IGF-1 pathway can be an effective target to ameliorate cardiac function [35, 36], Another important cell signaling regulator in the heart failure process is mTOR. Overexpression of eIF4E in this signaling pathway can lead to impairment in cardiac function. Therefore, the mTOR/eIF4E signaling pathway also a great influence on the aging process of the heart [29].

SIRTs are a conserved family of NAD^+-dependent deacetylases (class III histone deacetylases). Additional copies of the *Sirt* gene in fermentation were associated with increased longevity [29–31]. There are seven SIRTs subtypes in mammals, sirt1-7. Sir2 controls the extension of replication life under the effect of DR (decreased glucose) [32, 33]. Mice lacking SIRT1 showed shorter life span compared with peers. In addition, SIRTs also taken important regulatory role in mitochondria of cardiomyocytes. Sirt3 was reported expression decreases with age in people who have been sedentary for a long time, and can be increased after endurance training [34]. The low to medium expression of Sirt1 in the heart can reduce the age dependence of cardiac hypertrophy, cardiac dysfunction and aging markers. Besides, SIRT3 knockout showed signs of accelerated aging, including myocardial hypertrophy and accelerated fibrosis [35]. Increased SIRT3 expression was associated with longer human lifespan [36]. SIRTs are involved in nutritional signal transduction and epigenetic regulation of histone deacetylation and DNA expression directly related to cardiac aging. This is consistent with the growing recognition of the epigenetic modifications in aging [37] and cardiovascular disease [38]. DNA hypomethylation is link with cardiovascular disease risk [39].

2.2.2 Abnormal Mitochondrial Function

Studies have been suggested that the accumulation of mitochondrial reactive oxygen species (ROS) would cause damage of mitochondrial DNA and proteins, leading to dysregulation of cellular activity, organ dysfunction, and ultimately limiting health and lifespan [40]. Besides, ROS production in the heart increases significantly in age [41]. Mitochondrial ROS can lead to mitochondrial dysfunction and cardiomyopathy in the elderly [42, 43]. In addition, abnormal overexpressed catalase-targeted mitochondria is clearly detected in the aging heart of mice, which is the most direct evidence of mitochondrial oxidative damage leading to cardiac aging. Therefore, decreasing mitochondrial oxidative

damage is one of the important strategies to prevent heart aging. Further studies have shown that peroxisome proliferator-activated receptor gamma coactivator 1α (PCG-1α) is a major molecule in regulating mitochondrial function. Overexpression of PCG-1α can ameliorate the function of mitochondrial in the myocardium. Thus, interfering PCG-1α expression might be an effective way to alleviate the occurrence of mitochondrial oxidation [44]. Knockout PCG-1α in mice, the mitochondrial gene expression was reduced but developed cardiac dysfunction [45]. In adult mice, PCG-1α overexpression was directly associated with cardiomyopathy [46].

Some studies have shown that mitochondrial dysfunction increases with age, which is associated with abnormal production of mtROS [42, 43, 47]. For example, reduced mitochondrial oxidative phosphorylation is associated with reduced activity of electron transport complexes I and IV, while compounds II, III, and V are relatively unaffected [48]. Damage to electron transport function may be result in increased electron leakage and mtROS generation. Mitochondrial energy dysfunction resulting from mitochondrial decoupling, decreased substrate availability [49] and increased mitochondrial DNA deletion have been demonstrated in human and experimental heart failure animals [50, 51].

2.2.3 Neurohormonal Regulation

Renin-angiotensin aldosterone system (RAAS) is an important system regulating hypertension and is associated with cardiovascular disease and age-related failing in cardiac function [52]. The concentration of Ang II in the heart significantly increased with age, and many structural, functional and molecules alterations consistent with the action of Ang II were found in the elderly heart [12, 53]. Inhibitor captopril or angiotensin receptor I inhibitor could reduce myocardial fibrosis and fibrosis-related arrhythmias in older mice [54]. And destroy angiotensin receptor type I would extend the lifespan [55]. RAAS is associated with tissue aging in a variety of tissues. Such as in kidneys, angiotensin blocking was beneficial for kidney aging [56].

Epinephrine have adverse effects on cardiovascular health. β-adrenergic signaling pathway is associated with aging, and adenylate cyclase 5 can significantly improve the effects of age-related cardiac dysfunction, and lifespan [57–59]. With increasing evidence supporting that the important role of epinephrine is mediated by mitochondrial ROS [60]. The increase of ROS plays an important role in β adrenalin. Although β-adrenergic antagonists are commonly used in heart disease [61], their effect on longevity has not been evaluated. To determine a safety and effective approach, these inhibitors are combined with other signaling pathways inhibitors for maximum positive effect.

Insulin-like growth factor (IGF) signaling is another important element of longevity. Lack of the insulin-like receptor extends the lifespan of mammals [62, 63], and could reduce the specific benefits of the IGF-1 signaling pathway for heart aging in mouse models [64, 65]. Unfortunately, the role of IGF-1 signaling in human heart aging is complex. IGF-1 levels significantly decreased with age, and in elderly patients without a history of heart disease, low serum IGF-1 levels are associated with an increased risk of heart failure [66]. In growth hormone therapy, IGF-1 pathway was proposed to be beneficial for heart failure patients [67]. Insulin activates a phosphorinosine-3-kinase (PI3K) signaling cascade that phosphorylates and activates AKT. Activated AKT is transferred into the nucleus, and then inhibit the transcription activity of FOXO by phosphorylation. In the heart, the FOXO family is link with oxidative stress [68], metabolic regulation [69], and apoptosis [70]. FOXO transcription factor has an anti-aging effect, therefore, inhibiting insulin signaling or overexpression of FOXO can prevent cardiac function from declining with ageing [65].

3 Noncoding RNAs (ncRNAs)

In the early of the molecular biology, RNA was divided into two groups: protein-coding RNAs and functional RNAs, such as ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), small

nucleolar RNAs (snoRNAs), and transfer RNAs (tRNAs). With the development of transcriptome, especially the innovation of RNA-sequencing, more and more ncRNAs have been discovered. The study of RNAs from protein-coding RNAs to ncRNAs. Many ncRNAs, demonstrated new regulatory function. Considering the complexity of such ncRNAs in structures, genomic orientation, function, cellular localization, or other emerging criteria, a simple and common ncRNAs classification was needed to be raised. The most well-accepted classification model was based on the length of RNA: (1) small RNAs, the transcripts are shorter than 200 nt, including microRNAs (miRNAs, miRs). (2) long noncoding RNAs (lncRNAs), the transcripts are longer than 200 nt. In addition, a class of special lncRNA, circular RNA (circRNA), which is covalently closed, single-stranded RNA molecules, recently obtained much attention. These ncRNAs display distinct temporal and spatial expression patterns, and almost involved in all biological processes [71]. As details of the impact of ncRNAs on molecular and cellular processes are becoming better understood, their roles in aging-associated physiologic processes and disease conditions are also starting to emerge. Some ncRNAs have a connection between cardiac aging (Fig. 14.1). The research of ncRNAs in aging-associated heart dysfunction provides new perspective in deeper insights into disease mechanisms and innovative therapeutic strategies.

4 MiRNAs in Cardiac Ageing

MiRNAs are single-stranded RNAs ~22 nt in length and found in both the intergenic and coding regions of the genome. The primary miRNAs (pri-miRNAs) are transcribed from both intronic and exonic regions by RNA polymerase II. Then the pri-miRNAs are processed to precursor miRNAs (pre-miRNAs) in nucleus by Drosha and DGCR8. The pre-miRNAs were stem-loop

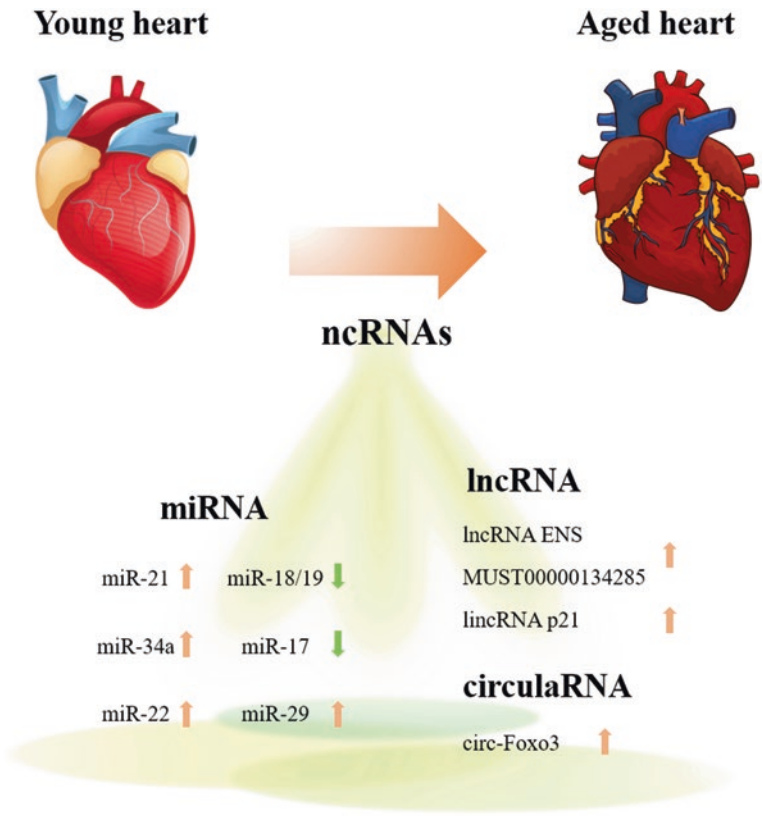

Fig. 14.1 Noncoding RNAs in cardiac ageing

structures with ~70 nt long. The pre-miRNAs exported to cytoplasm from nucleus with the assistance of exportin-5. In cytoplasm, the stem-loop structures cleaved by Dicer and turn into a mature miRNAs with ~22 nt length. Classically, miRNAs repress the expression of their target mRNA by binding to the specific untranslated regions (UTRs) based on complementary base pairing. The single stranded miRNA, associated with Ago, assembled into the RNA-induced silencing complex (RISC), miRNA–RISC complex induces translation inhibition and mRNA degradation, result in mediates post-transcriptional repression of a target mRNA. In this mode, miRNAs can regulate all physiological and pathological processes.

Some miRNA arrays or miRNA profiling were performed to identify the dysregulated miRNAs in the hearts of young and aged mice. 65 miRNAs changed over 1.5-fold in aged heart, among them, 34 miRNAs were up-regulated while 31 were down-regulated [72]. Addition, the expression of the miRNA machinery proteins Ago1 and Ago2 were also found to be increased with age, and synergistically induced miR-21 and miR-21∗ in ageing. MiR-21was involved in myocardial diseases [73]. MiR-21 was up-regulated in left ventricular myocardium, myocardial hypertrophy and failing human left ventricular myocardium. Also, miR-21 was enriched in fibroblasts, and increased in fibroblasts of failing heart, inhibiting ERK-MAP kinase pathway via inhibiting Spry1. Inhibiting miR-21 by antagomir in vivo could reduce fibrosis and attenuate cardiac dysfunction. Interestingly, miR-21 was also found to be increased in 15-month old mice compared with 2-month old mice [74]. Overexpression of miR-21 promoted Dox-induced cardiomyocytes, whereas miR-21 knockout mice demonstrated the ability of resist to Dox-induced cardiac alterations. Mechanistically, PTEN was a target gene of miR-21 involved in D-gal and Dox-induced cardiac senescence.

From another miRNA profiling, Reinier A. Boon found that miR-34a was up-regulated in ageing heart, and significantly correlated with age in human heart biopsies [75]. Inhibit the expression of miR-34a would prevent age-related and myocardial infarction-induced cardiomyocytes death and improve cardiac function. Pnuts was the target gene of miR-34a that mediated age-induced cardiac cell death and functional decline. miR-34a has also been reported to be involved in the repair and regeneration of myocardial infarction in neonatal mice, increasing the level of miR-34a could suppress the neonatal cardiomyocytes reentry into cell cycle and reduce the survival rate of neonatal cells [76]. Also, miR-34a has been reported to mediate a variety of myocardial injuries [77–80]. Some new therapies have been developed by inhibiting the expression of miR-34a, such as miRNA sponges and drug interventions [81, 82]. In addition, miR-22 was also found to be elevated in 19 months old mice [83]. Overexpression of miR-22 would induce cellular senescence and promote migratory activity of cardiac fibroblasts via inhibiting mimecan.

Accumulation of the extracellular matrix (ECM) are recognized as a key feature of cardiac ageing [84]. miR-17-92 cluster has been proved taken the crucial role in regulating matrix genes in ageing cell [85]. Among them, miR-18 and miR-19 were down-regulated in ageing induced heart failure and regulated the fibrosis in ageing cardiomyocytes through miR-18/19- CTGF/TSP-1 axis [86] MiR-17, another member of miR-17-92 cluster, was also reported to participate in cardiac ageing [87]. Unlike miR-18 and miR-19 mainly expressed in cardiomyocytes, miR-17 was expressed in ageing cardiac fibroblasts and inhibited the cellular senescence and apoptosis of fibroblasts via targeting par4. Furthermore, miR-17 transgenic mice suppressed mouse cardiac senescence. Additionally, TGFβ-Smad signaling is one of the prominent pathways both involved in fibrosis and senescence [88–91] TGFβ-Smad regulates expression of miR-29 (miR-29a, miR-29b and miR-29c), which mediated the reduction of H4K20me3 through targeting Suv4-20 h, leading to premature cellular senescence and cardiac dysfunction [92].

5 Long Noncoding RNAs in Cardiac Ageing

LncRNAs are defined as being ncRNA sequences of >200 nucleotides. LncRNAs are transcribed by RNA polymerase II or III, may be multi-exonic, 5′-capped, and poly-adenylated. According to their genomic location, lncRNAs have been classified into six categories, which is intergenic, intronic, bidirectional, enhancer, sense, and antisense lncRNAs. LncRNAs localized in the nucleus or cytoplasm where they may regulate gene expression at transcriptional or posttranscriptional levels, respectively. Briefly, when lncRNA located in nuclear, the regulated models of lncRNA acted as signal, decoy, guide, scaffold or enhancer [93]. While the cytoplasm-localized lncRNAs were usually mediates the stability the ribonucleoprotein complexes and mRNA, as well as sponge miRNAs [94]. Especially, some lncRNAs hold the ability to encode small peptides, such as LINC00961, LOC100507537 (NONMMUG026737 in mice) and LINC00948 (2310015B20Rik in mice) [95–97]. LncRNAs extensively participates in physiological processes such as cell proliferation, hypertrophy and metabolic regulation. The dysfunction of lncRNA is closely related to the occurrence of tumors and other diseases [98–102]. Specifically, SAL-RNA1, H19 and lncRNA Chronos involved in regulating senescence [103–105]. However, there are few studies on lncRNA in cardiac aging have been reported.

Detected by lncRNA/mRNA microarray, a total of 1957 lncRNAs and 984 mRNAs were found to be uniquely differentially expressed between young and aged heart tissue. Among then, lncRNA (ENSMUST00000134285) was increasing in aged heart as well as aged cardiacmyocytes. Overexpression of lncRNA (ENSMUST00000134285) significantly reduced cardiomyocyte apoptotic. LncRNA (ENSMUST00000134285) was co-expressed with MAPK11 and promoted MAPK11 via miR-760 [106]. Besides, lincRNA-p21 was investigated in Dox-induced cardiomyocytes senescence. Knockdown of lincRNA-p21 was significantly increased the cellular viability and decreased the cell cardiomyocytes senescence via regulation of senescence-related genes p53 and p16. Furthermore, the pro-senescent effect of lincRNA-p21 via Wnt/β-catenin signaling pathway [107].

6 Circular RNAs in Cardiac Ageing

Circular RNAs (circRNAs) is a special type of lncRNAs. They are generated from either intron or exon. Its specialty lies in forming a loop without 5′-3′ polarity or polyadenylated tail through back splicing of the 5′ and 3′ ends after transcribed from genomic DNA. The regulation mechanisms of circRNAs have been revealed by increasing studies. Such as miRNA sponges, binds to RNA binding proteins (RBPs), competes with canonical pre-mRNA splicing in gene regulation, and translated [108]. CircRNAs have been identified as crucial regulators of diverse cellular processes [109]. Only one circRNA was reported to involved in cardiac senescence so far [110]. Circ-Foxo3 was found to be up-regulated in old heart patients, older mice and H_2O_2 treated primary cardiomyocytes. In Dox-induced cardiomyopathy, in vivo overexpression of circ-Foxo3 could worsen the heart function, myocardial hypertrophy and myocardial fibrosis, whereas repressed circ-Foxo3 would reverse that. Also, in vitro, circ-Foxo3 overexpress could worsen cellular senescence independent of linear Foxo3. Specifically, circ-Foxo3 could bind to senescence-related proteins ID1 and E2F1, and stress-related proteins HIF1a and FAK in cytoplasm. Result in its associated proteins arrest in cytoplasm and abolished the transcriptional regulation, and induced cellular senescence in heart.

7 Conclusion

With elderly population in the world increases, ageing-related diseases are attracting more and more attention. Aging increases the risk of cardiovascular disease, thus there is an urgent need to reveal the underlying mechanisms of cardiac

ageing. As we discussed here, some ncRNAs have been reported to involved in cardiac ageing. However, the researches focus on cardiac ageing obviously fewer and more efforts definitely need to be taken. Besides, the circulating ncRNA (miRNAs, lncRNAs and circRNAs) have been proposed to serve as biomarkers in many diseases. Unfortunately, there is no research on cardiac ageing so far. Further studies taken into this aspect should be of great interests. In conclusion, ncRNAs have been demonstrated to be excellent therapeutic targets in many diseases, and more depth and extensive investigations in cardiac ageing should be of great significant.

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