REVIEW

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Roles of microRNA in vascular diseases in cardiac and pulmonary systems

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Coronary artery disease (CAD) and pulmonary arterial hypertension (PAH) are two of the most dangerous vascular diseases. Their etiology and pathogenesis are not yet fully understood, thus it remains difficult to achive great advance in the diagnose, therapy and prognosis techniques. microRNAs (miRNAs), a class of highly conserved, small, noncoding RNAs, critically mediate the post-transcriptional gene modulation, which regulates an array of important physiopathological processes including those occurring in cardiac and pulmonary systems. Thereby manipulation of miRNA expression could potentially be applied therapeutically. In this review, we summarize the current knowledge on the roles of miRNAs in the development of vascular diseases, especially in CAD and PAH, providing a theoretical basis for potential uses of miRNA in diagnosis, prognosis, and therapy in these cardiovascular diseases.

1. Introduction

Recently, coronary artery disease (CAD) and its associated serious complications such as myocardial infarction have become the main cause endangering human health, as so it is named as "the first killer of mankind" (Wang 2005). Specially, approximately 80% of all sudden cardiac deaths are caused by coronary atherosclerosis (AS) with the rest of 20% resulting from cardiomyopathy, left ventricular hypertrophy, Brugada syndrome and others (Zipes and Wellens 1998). Pulmonary arterial hypertension (PAH) is another deadly vascular disease primarily resulting from increased arterial pressure (mean value $\geq$ 25 mmHg) and vascular resistance in the pulmonary arteries, which may ultimately lead to right heart failure or even death (Lourenço et al. 2012). These serious heart and lung diseases are difficult to diagnose and have poor prognosis, as so they are deemed as cancer in cardiovascular diseases (Agarwal and Gomberg-Maitland 2011; Oishi et al. 2011). Thus, understanding etiology and pathology of these vascular diseases occurring in heart and lung are extremely important to develop effective therapies and to reduce morbidity and mortality of these vascular diseases.

Both CAD and PAH are believed to be the interactive results of multiple factors such as gene mutation, genetic heterogeneity, racial differences and economical factors, in which a large number of genetic susceptible genes play an important role (Wang 2005; Satoh et al. 2006; Oishi et al. 2011; White et al. 2012). The current diagnosis of CAD and PAH is limited by measuring serum specific sensitive factor, electrocardiogram, physical detection and other few means. These techniques can only be applied when AS develops to a certain extent with occurrences of abnormal vascular remodeling, insufficient blood supply, angina and even myocardial infarction. The current available drugs and surgery approaches can just alleviate patient's pain and delay the onset of disease; however, none can stop the development of these deadly diseases. Therefore, early diagnosis is the key to effectively prevent and treat CAD and PAH, improving the cure rate and survival rate of the patients.

Increasing evidence has shown that microRNAs (miRNAs) as signal pathway control factors play an important role in vascular diseases in the heart and lung vasculature (Humbert et al. 2008; Chan and Loscalzo 2011; Fiedler et al. 2011). Thus, we are reviewing molecular mechanisms and clinical applications of miRNA in the pathological processes of vascular diseases with specific focus on CAD and PAH.

2. miRNAs

miRNAs are a cluster of a 21$\sim$25 nucleotides endogenous non-coding single-stranded RNA molecules, which inhibit expression of their target genes by degradating the mRNA or inhibiting the transcription (Bartel 2004; Jing et al. 2005). In general, a miRNA can control multiple mRNAs, while an mRNA may also be targeted by different miRNAs. This results in the multiplicity, complexity and network of gene regulation. As more and more miRNAs are discovered and the number of publications related to the miRNA biology has increased dramatically over the past decade, implying the incremental importance of these regulators in human health and disease (Fig. 1). Currently, approximately 1400 human miRNAs are identified, the roles of more than 700 have been determined so far (Esteller 2011). They participate in regulating transcription and expression of 50%$\sim$60% of the function genes involving many critical biological processes such as cellular differentiation, proliferation, apoptosis, metabolism, and growth (Lewis et al. 2005; Friedman et al. 2009). Moreover, the miRNAs have been found to have extensive use in disease diagnosis, drug screening, and gene therapy (Anand et al. 2010).

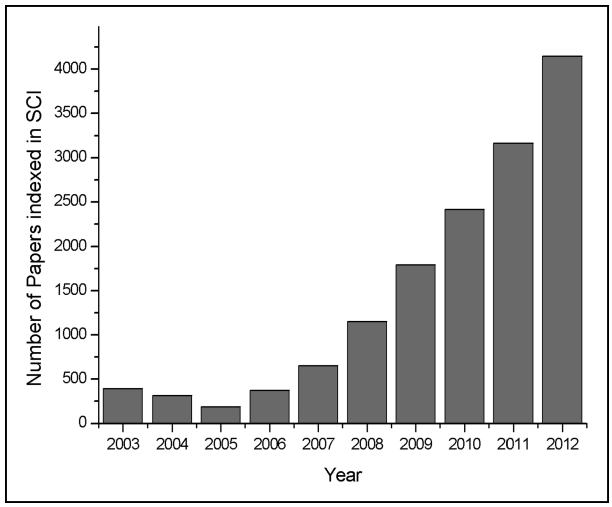

Fig. 1: The number of publications related to miRNA biology. The data of paper numbers were from the Web of Science database from 2003 to 2012.

Since 2005, attention has been drawn to potential use of miRNAs in the cardiovascular system of mammals, particularly regarding their involvements in regulation of growth of myocardial and vascular cells, coupled with subsequent ventricular wall integrity, myocardial movement, and heart rhythm, especially since it has been shown that abnormal expression of miRNAs can lead to vasculature remodeling, cardiac dysfunction and pulmonary disorder, etc. (Esquela-Kerscher and Slack 2006; Urbich et al. 2008; van Rooij et al. 2008).

3. miRNA in vascular diseases

An increasing number of miRNAs have been reported to significantly affect vascular development and function (Urbich et al. 2008). In these miRNA, miR-126, the first miRNA cloned from vascular endothelial cells, is known to plays an important role in maintaining blood vessel integrity as shown in mice and zebrafish models (Fish et al. 2008; Wang et al. 2008; Kuhnert et al. 2008). miR-126, located in the intron region of epidermal growth factor domain, can inhibit smooth muscle cell and endothelial cell migration (Soncin et al. 2003; Campagnolo et al. 2005; Schmidt et al. 2007; de Mazière et al. 2008; Musiyenko et al. 2008). In contrast, miR-126 may also improve the VEGF and FGF activity by inhibiting expression of negative control factor (Sprouty-related EVH-1 domain containing-1, SPRED-1) and PIK3R2, so as to promote angiogenesis and maintain the integrity of the vasculature (Wang et al. 2008). Moreover, inhibiting of miR-126 can enhance TNF-á induced VCAM-1 expression and promote the hemamebus to adhere to the endothelial cells, leading to vascular remolding and pathological changes (Harris et al. 2008).

Another miRNA, miR-21 is also considered as an important regulator in CAD and PAH pathogenesis. A recent study has shown that the miR-21 level increases significantly in the peripheral blood from CAD patients associated with a high content of plasma asymmetrical dimethylarginine (ADMA), indicating that ADMA inhibited vascular angiogenesis *via* miR-21 (António et al. 2010). High expression of miR-21 was also detected in the foam-like injured vascular wall; however, after miR-21 knockout, intima damage and proliferation degree was alleviated and accompanied with an increase in apoptosis (Ji et al. 2007). Cheng et al. (2009) found that miR-21 down-regulation suppressed cell proliferation and embryonic development induced by the myocardial hypertrophy promoting factors. The mechanism of miR21 suppression in myocardial cell proliferation and embryonic development may be related to the mitogen-activated protein kinases (MAPK) signaling pathway. In addition, a recent study has reported that shear stress induced miR-21 expression and enhanced eNOS activity, reducing the endothelial cell apoptosis (Weber et al. 2010). Meanwhile, miR-21 was identified as a PAH-modifying miRNA, regulating targets integral to bone morphogenetic protein (BMP) and Rho/Rho-kinase signaling as well as functional pathways associated with hypoxia, inflammation, and genetic haploinsufficiency of BMP receptor type 2 (Parikh et al. 2012; Ahmad et al. 2012). Together, these results clearly indicate the importance of miR-21 in myocardial and endothelial cells, suggesting that inhibition of miR-21 could potentially be useful for prevention and control of AS related vascular diseases.

Indeed, myocardial ischemic damage induced by the coronary ischemia in CAD patients is closely associated with differential miRNA expression and regulation. For instance, ischemia preadaptation in rats can up-regulate 21 miRNAs and down-regulate 19 miRNAs (Cheng et al. 2010). Among these differentially expressed miRNA, miR-21 with a highest up-regulation level may participate in myocardial ischemic damage by promoting or attenuating the expression of matrix metalloproteinase-2 (MMP-2) by targeting the phosphatase and tension protein homologue protein (PTEN) (Roy et al. 2009; Cheng et al. 2010). Yin et al. have also demonstrated that injection of miR-320 into the heart of mice robustly reduced myocardial infarction areas *in vitro* reperfusion, plausibly through down-regulating HSP20 protein (Yin et al. 2008; Ren et al. 2009). To evaluate the therapeutic efficacy and antiremodeling potential of miRNA inhibitors in the pathogenesis of PAH, a latest paper confirmed that inhibition of miR-17 improved lung and heart function in experimental pulmonary hypertension (Pullamsetti et al. 2012).

In addition to miR-21, many other miRNAs can also affect the pathogenesis of vascular diseases in cardiac and pulmonary systems. These miRNA include miR-206, miR-145, miR-143 and miR-221, all of which have been shown to regulate vascular smooth muscle cell proliferation, migration and differentiation, affecting vasculature phenotypic building (Cordes et al. 2009; Boettger et al. 2009; Davis et al. 2009; Liu et al. 2009; Cheng and Zhang 2010; Caruso et al. 2012; Jalali et al. 2012). Moreover, miR-204, miR-155, miR-146 and miR-125a-5p regulated the vascular pathological reaction depending on the related mononuclear cells and inflammatory factor (Taganov et al. 2006; Ceppi et al. 2009; Chen et al. 2009; Shen et al. 2010; Courboulin et al. 2011).

4. miRNA in application of early diagnosis

As miRNA has been widely used as a useful biomarker in cancer and other diseases, the early diagnosis of vascular diseases including CAD and PAH is also believed to be the optimal approach. Indeed, In the plasma of animal models and clinical patients with acute myocardial infarction, miR-1, miR-133a, miR-133b and miR-499-5p levels are significantly elevated as compared to the control group, and they restored to normal five days later, the peak of the former three appeared earlier than troponin I (TnI), and the peak of the last one was later than TnI (D'Alessandra et al. 2010). Moreover, the miR-134, miR-135, miR-198 and miR-370 levels are also much higher in the unstable angina pectoris patients, than that in the stable group, in among which miR-135 enhanced by 19 folds but miR-147 was poorly expressed, which suggested that the miRNA can be used for risk assessment and early prediction of acute CAD (Hoekstra et al. 2010). Other researchers revealed that some miRNAs from peripheral circulation blood can be used as disease biomarkers for they showed strong sensitivity and specificity in tissue

Table: miRNAs and its function in vasculature diseases

miRNA	Related function
miR-145	Smooth muscle cell differentiation, phenotype changes
miR-199b	NFAT/calcineurin signaling
miR-24	Apoptosis, migration
miR-320	Apoptosis
miR-126	Smooth muscle cell differentiation, phenotype changes
miR-499	Apoptosis
miR-29	Cardiac fibrosis
miR-133	Pacemaker hyperpolarization
miR-1	Spontaneous calcium current, potassium channel
miR-17	TGF-signaling, proliferation, cell survival
miR-21	Cell growth, apoptosis, angiogenesis, proliferation, cell cycle, fetal gene reprogramming, APC migration, MAPK/ERK signaling
miR-204	NFAT signaling, proliferation, apoptosis
let-7 family	Cell cycle, proliferation
miR-27a/b	Proliferation, drug metabolism, differentiation
miR-30c	Matrix remodeling, cardiac hypertrophy
miR-130	Survival, cell growth
miR-145	Cell death, differentiation, vascular smooth muscle plasticity, cytoskeletal remodeling
miR-210	ROS signaling, angiogenesis, cellular metabolism
miR-224	TGF signaling, proliferation, apoptosis
miR-451	Erythropoiesis

damage and pathological conditions (Mitchell et al. 2008; Skog et al. 2008). However, it is essential to carry out a great deal of work on miRNAs to explore early diagnostic tools in the clinical practices. On the one hand, it is urgent to explore more effective susceptibility genes and target molecules, and to establish the relevance with vasculature disease mechanism so as to be applied in the early diagnosis and accurate prognosis of CAD and PAH. Moreover, technical obstacles such as high detection cost, poor repeatability and easy degradation of small molecule miRNA also need to be overcome.

5. miRNA in clinical treatment

As more miRNAs and their functions were identified in vasculature, the application of miRNA in clinical treatments of CAD and PAH has drawn increasing attention. The usual treatment strategy is to regulate miRNA transcription or its structure stability, modulating miRNA levels, ultimately altering its downstream gene networks and signal pathways.

Currently, the main treatment strategies are listed as follows: (1) necessary means should be taken to enhance expression of certain miRNA, which are known to be down-regulated during the disease state. miRNA simulative technology could be adopted, that is, the mimic double-stranded RNA can be synthesized based on the endogenous miRNA sequence, and then introduced into the body to maintain the miRNA level (Wolfrum et al. 2007); (2) knocking out or silencing the target miRNA which are known to be overexpressed in the pathological process. One way to do so is to use a target miRNA complementary antisense oligonucleotide chain, whose 3' end is coupled with a cholesterol molecule to improve its inhibition effect; alternatively, one could use the miRNA sponge technology to introduce many repeated copy and incomplete complementary oligonucleotide chain by the slow virus carrier into the body (van Rooij et al. 2008).

Increasing evidence from animal models supports clinical application of miRNA. For example, it has been shown that injection of miR-122 specific antagonist into obese mice, robustly decreases the cholesterol content in the plasma and significantly reduces liver steatosis (Boettger et al. 2009). Recently, in rat balloon injury carotid artery model transfection of miR-145 carried in the adenovirus successfully inhibits the formation of neointimal damage (Esau et al. 2006). These results strongly suggest that miRNA can be used as therapeutic target of vasculature diseases, although the feasibility of clinical application encounters more challenges, such as targeting transport and distribution of miRNA drug to target cells, clinical intervention methods and drug safety and gene therapy ethics.

In conclusion, vasculature diseases including CAD and PAH is considered to have the highest mortality rates all over the world. As evidenced by a number of previous reports, miRNA can greatly impact on the pathological process of the disease, providing a new, promising strategy for the disease diagnosis, prevention and treatment (Drake et al. 2011). However, because miRNA-related studies in the cardiovascular medical field were started just a few years ago, relevant knowledge is limited and much more research is required before miRNA can be used clinically (Dangwal et al. 2012).

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