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MicroRNA-1 in Cardiac Diseases and Cancers

Jianzhe Li[1], Xiaomin Dong[2], Zhongping Wang[3], and Jianhua Wu[4]

[1]Department of Pharmacy, Ruikang Hospital, Guangxi University of Chinese Medicine, Nanning, Guangxi 530011, [2]Department of Osteology, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, [3]Department of Physiology and pathophysiology, school of Basic Medical Sciences, Jiujiang University, Jiujiang, Jiangxi 332000, [4]Department of Pharmacy, Zhongnan Hospital of Wuhan University, Wuhan, Hubei 430071, China

MicroRNAs (miRs) are endogenous ≈22-nt non-coding RNAs that participate in the regulation of gene expression at post-transcriptional level. MiR-1 is one of the muscle-specific miRs, aberrant expression of miR-1 plays important roles in many physiological and pathological processes. In this review, we focus on the recent studies about miR-1 in cardiac diseases and cancers. The findings indicate that miR-1 may be a novel, important biomarker, and a potential therapeutic target in cardiac diseases and cancers.

Key Words: Cancers, Cardiac diseases, MicroRNA-1

INTRODUCTION

MicroRNAs (miRs) are a group of endogenous ≈22-nt non-coding RNAs that participate in the regulation of gene expression through binding to the 3'-untranslated regions (UTRs) of target mRNA at post-transcriptional level [1]. MiRs were first discovered in the nematode Caenorhabditis elegans by Rosalind C. Lee in 1993 [2]. Since then, abundant miRs were found in many species such as plants, animals and human being [3-5], and regarded as a class of highly conserved RNA in the course of evolution. So far, more than 1000 miRs are predicted in human genome, and regulate about 30% of human genes [6,7]. There is growing evidence that miRs play important roles in various physiological and pathological processes, including cardiogenesis, neural differentiation, cell apoptosis and tumor formation, etc [8-10]. Among the known miRs, miR-1 is one of the muscle-specific miRs, and highly expressed in cardiac tissue [11].

MiR-1 is encoded by two nearly identical genes: miR-1-1 and miR-1-2, which are located within intron 2 of an uncharacterized gene C20ORF166 and intron 12 of the E3 ubiquitin-protein ligase MIB1 (Mindbomb Homogog 1) on chromosomes 20 and 18, respectively [12,13]. Both miR-1-1 and miR-1-2 give rise to identical mature miR-1 species and appear to target the same mRNAs [14-16]. Targeted deletion of miR-1-1 results in a phenotype similar to that described for miR-1-2-null mice [14]. Accordingly, mice that lack of the miR-1-2 gene will lead to various heart abnormalities, but generally survive because they still generate some miR-1 from their remaining miR-1-1 gene [12]. When lacking both miR-1-1 and miR-1-2, mice will appear more profound abnormalities and die before weaning [8,12].

It has been reported that over-expression of miR-1 in the developing heart resulted in a decreased pool of proliferating ventricular cardiomyocytes through reducing the protein levels of Hand2, a transcription factor that promotes ventricular cardiomyocyte expansion [15]. In miR-1-2-null mice, the hearts have a series of abnormalities, including ventricular septal defect, cardiac rhythm disturbances and a striking myocyte cell-cycle abnormality [8]. These findings suggest that the proper expression of miR-1 is necessary for cardiogenesis and maintenance of the normal heart function. Changes in miR-1 expression would lead to the occurrence of many cardiac diseases.

In addition to the pathophysiological roles of miR-1 in cardiac diseases, many studies have also demonstrated that aberrant expression of miR-1 plays important roles in the initiation, development and metastasis of human cancers [17]. A large number of studies have shown that miR-1 expression is frequently down-regulated in several cancer types, which results in the up-regulation of multiple oncogenes including Slug, MET and transgelin 2 (TAGLN2), etc [18]. Restoration of miR-1 expression or transfecting miR-1 was able to significantly inhibit tumor cell proliferation, migration and invasion [18,19]. The over-expression of miR-1 has also been reported to induce tumor cell apoptosis by activating caspases-3, a key enzyme in the apoptosis cell-

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Corresponding to: Jianhua Wu, Department of Pharmacy, Zhongnan Hospital of Wuhan University, Dong-Hu Road #169, Wuhan 430071, China. (Tel) 86-27-67813199, (Fax) 86-27-67812892, (E-mail) wujianhua122012@126.com

ABBREVIATIONS: miR, microRNA; UTR, untranslated region; TAGLN2, transgelin 2; MI, myocardial infarction; IR, ischemia-reperfusion; miR-1-ES, transplanting miR-1 transfected embryonic stem cells; STEMI, ST elevation myocardial infarction; RasGAP, Ras GTPase-activating protein; Cdk9, cyclin-dependent kinase 9; PNP, purine nucleoside phosphorylase; XPO6, exportin-6.

signaling cascade [20]. The above investigations suggested that miR-1 function as a tumor suppressor. Therefore, increasing miR-1 expression may be an effective strategy for prevention of the initiation and development of cancers.

MiR-1 AND CARDIAC DISEASES

MiR-1 and arrhythmia

Arrhythmia is one of the major reasons for sudden cardiac death. Recently, several studies have observed that the abnormal expression of miR-1 is involved in occurrence of arrhythmia. Girmatsion et al. [21] reported that the levels of miR-1 were greatly reduced in left atria from patients with persistent atrial fibrillation. While the mRNA and protein expression of inwardly rectifying potassium channel 2.1 (a target of miR-1) was significantly increased, which led to increased inwardly rectifying potassium current. In rat ventricular myocytes, over-expression of miR-1 can inhibit the protein phosphatase PP2A regulatory subunit B56α, which could enhance the functional activity of RyR2 channels and thus result in increased cardiac excitation-contraction coupling gain, elevated diastolic sarcoplasmic reticulum Ca^{2+} leak, and reduced sarcoplasmic reticulum Ca^{2+} content and promote arrhythmogenic disturbances in myocyte Ca^{2+} cycling [22]. In addition, Zhao et al. [8] found that deletion of miR-1-2 resulted in severe arrhythmia through up-regulating the expression of Irx5, a member of Iroquois family of homeodomain-containing transcription factors that regulates cardiac repolarization by repressing Kcnd2 (a key potassium channel) [23].

MiR-1 and myocardial infarction

Many recent studies have shown evidence for the role of miR-1 in myocardial infarction (MI). The level of miR-1 was significantly down-regulated both in MI patients and ischemia-reperfusion (IR) rat [24,25]. Transplanting miR-1 transfected embryonic stem cells (miR-1-ES) into the border zone of the infracted heart of c7BL/6 mice, the heart function was significantly improved after 2wk post-MI. The beneficial effect of miR-1-ES is attributed to protection of host myocardium from MI-induced apoptosis through activating p-AKT and inhibiting caspase-3, phosphatase and tensin homolog, and superoxide production [26]. More recently, reports show that miR-1 also exists in the circulating blood of humans and animals [27]. Under physiological conditions, miR-1 is present at very low levels in plasma. However, the level of miR-1 is significantly increased both in MI patients and mice [6]. Using a rat model of AMI, Cheng et al. [28] found that the serum miR-1 was rapidly increased after AMI with a peak at 6 h, and returned to basal levels at 3 day, there was a strong positive correlation between serum miR-1 level and myocardial infarct size. Circulating miR-1 in ST elevation myocardial infarction (STEMI) patients was increased 300-fold compared with healthy controls [29]. It is worth mentioning that increased circulating miR-1 was not related to age, gender, blood pressure, diabetes mellitus or the established biomarkers for AMI. Circulating miR-1, therefore, may be a novel, independent biomarker for early diagnosis of AMI [30].

MiR-1 and cardiac hypertrophy

Cardiac hypertrophy is a pathological condition and characterized by increased cell size, enhanced protein synthesis, and heightened organization of the sarcomere [31]. It is a persistent response of heart to a variety of harmful stimulation, including increased sympathetic nerve activity and pressure load [32,33]. Recent studies indicated that aberrant expression of miR-1 plays an important role in the development of cardiac hypertrophy. Both in rat hypertrophic left ventricle and phenylephrine-induced hypertrophic cardiomyocytes, miR-1 level was significantly decreased concomitantly with an increased expression of twinfilin-1(a cytoskeleton regulatory protein was identified as a potential target of miR-1), which stimulates hypertrophy through regulation of cardiac cytoskeleton. Further investigation found that silencing of endogenous miR-1 could induce cardiomyocyte hypertrophy. Whereas over-expression of miR-1 could reduce cell size and decrease the expression of hypertrophy-associated genes such as Acta1, Myh7 and Nppa, calmodulin, Mef2a, Ras GTPase-activating protein (RasGAP) and cyclin-dependent kinase 9 (Cdk9), etc [34-36]. These findings indicate that miR-1 exerts an anti-hypertrophic property.

MiR-1 and heart failure

Matured cardiomyocytes are the terminally differentiated cells, lacking of reproductive activity. The excessive apoptosis of cardiomyocytes would lead to the decreasing of cardiomyocytes, which is extensively recognized as an important mechanism of heart failure [37]. There is growing evidence that cardiomyocyte apoptosis is closely related to the abnormal expression of miR-1. It has been reported that treatment of cultured cardiomyocytes with H_2O_2 could significantly increase the rate of apoptotic cells concomItantly with up-regulated expression of miR-1. Further experiments found that over-expression of miR-1 aggravated H_2O_2-induced cardiomyocyte apoptosis, while inhibition of miR-1 using antisense inhibitory oligonucleotides resulted in significant resistance to H_2O_2 [38]. The miR-1 expression level was also markedly increased in the model of high glucose-induced cardiomyocyte apoptosis [39].

MiR-1 AND CANCERS

MiR-1 and rhabdomyosarcoma

Rhabdomyosarcomas are the most common soft tissue sarcomas in children [40]. Since the muscle-specific nature of miR-1, many studies focused on the roles of miR-1 in the development of rhabdomyosarcomas. Yan et al. [41] demonstrated that the miR-1 expression was significantly decreased in rhabdomyosarcomas compared with normal skeletal muscle, and presented at very low levels in a rhabdomyosarcoma cell line. At the same time, the expression of c-Met, a target of miR-1, was markedly up-regulated. There was a significant inverse correlation between miR-1 and c-Met expression. c-Met is a disulfide-linked heterodimer and encoded by MET oncogene [42,43]. The increased expression and activity of c-MET exist in different tumors, and contribute to tumor growth, invasiveness and metastasis [44]. In over-expression of miR-1 rhabdomyosarcoma

cells, the cell growth and migration was significantly inhibited, accompanied by the down-regulated expression of c-MET [41]. Decreased level of miR-1 in rhabdomyosarcoma cells was also proved by Rao et al. [40]. Meanwhile, they revealed that transcriptional profiling of cells after miR-1 expression exerts a strong promyogenic influence on poorly differentiated rhabdomyosarcoma cells.

MiR-1 and lung cancer

Lung cancer is still the number one cause of cancer-related death worldwide [45]. Since the 5-year survival rate was no more than 15%, it is necessary for early diagnosis and therapy of lung cancer. It has been reported that miR-1 was also expressed in lung, although at a lower level than in the skeletal muscle and heart [46]. There is evidence that miR-1 was significantly down-regulated in vinyl carbamate-induced mouse lung tumors [47]. Nasser et al. [20] also demonstrated that miR-1 level was markedly decreased in primary human lung cancer, including different histological types such as non-small lung cancers, adenocarcinomas, squamous cell carcinormas, large cell carcinoma and bronchoalveolar cell carcinoma. Consistent with the results in vivo, miR-1 level was almost undetectable in 16 lung cancer cell lines, which is relatively high in non-tumorigenic bronchial epithelial. Moreover, a recent study indicated that low serum expression level of miR-1 was related to unfavorable prognosis, and may be used as a biomarker to predict non-small-cell lung cancer survival [48].

MiR-1 and bladder cancer

Bladder cancer is seventh most common cancer in the world and the second most cancer of the genitourinary tract [49,50]. Although most of patients have a good clinical prognosis, about 50% of cases will suffer recurrence within four years of their initial diagnosis [51]. Therefore, elucidating the pathogenesis is helpful to prevent recurrence of bladder cancer. Recent studies found that the expression of miR-1 was significantly down-regulated in clinical bladder cancer specimens compared with normal bladder tissue [52]. In miR-1-transfected bladder cancer cell lines, the cell viability, migration and invasion were markedly inhibited, while the cell apoptosis was significantly increased [52,53]. To investigate the underlying anti-cancer mechanisms of miR-1, the authors observed the expression of TAGLN2 and LASP1, which were directly regulated by miR-1 and exert a potential oncogenic effect. The findings showed that the level of TAGLN2 and LASP1 was remarkably repressed in miR-1-transfected bladder cancer cell lines.

MiR-1 and prostate cancer

Recently, several studies have observed changes in expression of miR-1 in prostate cancer. Kojima et al. [54] reported that the expression levels of miR-1 were significantly decreased in prostate cancer compared with non-prostate cancer tissues. Restoration of miR-1 in prostate cancer cells could markedly suppress cell proliferation, migration and invasion. The beneficial effect of miR-1 was associated with regulation of purine nucleoside phosphorylase (PNP), which is identified as a new target of miR-1 and recognized as a potential oncogene. Ambs et al. [55] also demonstrated the down-regulation of miR-1 in prostate cancer, accompanied by increased exportin-6 (XPO6). This result was further verified in vitro, transfection of the prostate cancer cells with miR-1 could inhibit protein expression of XPO6.

Accumulating evidence indicate that dysregulated expression of miR-1 is a frequently event in cancers. In addition to the cancers described above, the abnormal expression of miR-1 was also found in other cancers, including colon cancer, hepatocelluar carcinoma, and head and squamous cell carcinoma, etc [56-58]. It is worthy to note that miR-1 expression was always down-regulated in all of these cancers. These investigations suggest that miR-1 may be a novel, potential target for tumor therapies.

CONCLUSION

MiR-1 is important in the development of heart and skeletal muscle. Dysregulated expression of miR-1 plays an important role in the pathogenesis of cardiac diseases and cancers. The underlying mechanisms are closely related to negatively regulation of its target genes, including Irx5, twinfilin-1, transgelin 2 and XPO6, etc. Although numerous studies have demonstrated the importance of miR-1 in cardiac diseases and cancers, and also recognized it as a novel, important biomarker and a potential therapeutic target, the exact role and mechanism of miR-1 is still not very clear due to the complexity of these diseases. More studies are needed to elucidate the role and mechanism of miR-1 in cardiac diseases and cancers.

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