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Mini Review

Micro-RNAs in the Heart: More than a Biomarker

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Abstract

Biomarkers of heart diseases are important in veterinary medicine because most cardiac conditions in dogs and cats are progressive, and some have a genetic basis. Biomarkers can be used either as a diagnostic tool or a therapeutic option. Several studies have been done on cardiac biomarkers, most of which investigated the role of pro-BNP and cardiac troponin I (cTnI) in heart diseases and congestive heart failure in dogs and cats [15]. Novel promising biomarkers [14], including Galectin-3 [10], heart-type fatty acid-binding protein (H-FABP) [13], soluble suppression of tumorigenicity 2 (sST2) [11], and micro-RNA (miRNA) [12] have been recently drawn attention to their role as prognostic or therapeutic factors in cardiovascular diseases of dogs and cats. Among these, MiRNAs, as will be explained in this writing, have a more distinguished place in human and veterinary cardiology [12].

Keywords: Micro; RNAs; Heart; Biomarker

Introduction

MicroRNA (miRNAs) are short, single-stranded, and non-coding RNAs that regulate or suppress gene expression by pairing to target mRNAs and degrading or preventing its translation [2]. MiRNAs consist of 18-22 nucleotides transcribed from DNA into primary precursor and mature miRNAs, respectively [1]. Based on miRbase (www.mirbase.org), about 2588 mature miRNAs have been identified in humans. In dogs, about 453 mature miRNAs have been reported to date. While miRNAs could be extracted from different tissues, cells, and blood, those quantified in specified cells would be more instructive [12]. For example, in valvular heart disease, the expression of different miRNAs may increase or decrease. Extraction of miRNAs from a particular cell and determining their changes could elaborate their role in the pathogenesis of a disease.

The different miRNAs' over or under expression have been evaluated in dogs and cats with heart disease in recent years. In dogs with myxomatous mitral valve disease (MMVD), significant dysregulation of miRNAs in various stages of disease (based on classification of the American college of veterinary internal medicine (ACVIM)) has been documented. In one study [6], the expression of 277 miRNAs in 18 dogs with and without MMVD was analyzed. In this study, changes in the expression of 11 miRNAs were recorded, four of which had been upregulated, and the remaining seven miRNAs had undergone down-regulation. This study showed significant differences in miRNAs expression between dogs suffering from stage B1/B2 and stage C/D of MMVD with those in stage A of the disease. In another study [9], the expression of miRNA-30b-5P in 13 cavalier King Charles spaniels suffering from stage B1 of MMVD and 11 healthy controls was investigated. Based on this

study, the plasma level of miRNA-30b-5P was significantly higher in dogs with stage B1 than those with stage A. This miRNA changed in the plasma of dogs at the occult stage of MMVD, especially at a young age. In another study [17], 291 miRNAs were measured in 5 dogs with stage C/D of MMVD and those with moderate to severe pulmonary stenosis (PS). All dogs suffered from eccentric (MMVD) or concentric (PS) ventricular hypertrophy. In another study [14] on 24 Dachshunds, including 16 dogs with stage B and C and 8 with stage A of MMVD, miR-30b and miR-133b were significantly down-regulated in stage B and stage C, respectively. In contrast to dogs with MMVD, dysregulation of miRNA in dogs with dilated cardiomyopathy (DCM) does not occur significantly. In a study of 8 Doberman Pinscher, including four healthy and 4 with DCM, different miRNAs' expression between two groups was not statistically significant [16].

Many questions about miRNA should be answered, and many investigations are actively trying to find answers to these questions. Some of the main questions are as follow [20]

- Identify the Particles which carry and protect miRNAs
- The number of miRNAs related to different types of particles
- The role and associations of these particles to ex-RNAs in health and disease
- Dysregulation of miRNAs in different tissue and cells in various diseases

In cardiovascular disease, finding a miRNA that can predict or diagnose the occult or asymptomatic phase of heart disease could be crucial. Nearly all heart diseases have an occult stage in which compensatory mechanisms in the body try to maintain cardiac function at an optimum level to cover body demands. At this stage, no clinical signs are present, and the patient seems healthy; however, physical examination and diagnostic imaging may disclose some aspects of the disease. For example, in dogs with occult stage MMVD, a systolic heart murmur would be heard over cardiac apex in auscultation. In echocardiography, blood regurgitation through the mitral valve is also apparent. Finding a biomarker that changes significantly during the occult stage of heart disease could help the clinicians slow down the further progression of the disease and the presence of congestive heart failure. In dogs with occult MMVD, pimobendane administration could significantly hinder stage C of the condition in which clinical consequences of cardiac decompensation, like pulmonary edema and cardiomegaly, would develop gradually. This increases the importance of the early diagnosis of MMVD in dogs. Dysregulation of miRNAs at the occult stage of MMVD in dogs (Stage B1-B2) could be investigated to find an early indicator of mitral valve endocardiosis to lower the progression rate of disease into stage C in which CHF and clinical signs of the disease occur.

Conclusion

MiRNAs could also play an exciting role in preventing and improving heart failure by inhibiting or reversing the mechanisms underlying cardiac remodeling and fibrosis. One of the essential pathological processes in various heart diseases is cardiac hypertrophy. MiRNA-1 has shown to have some inhibitory effects against cardiac hypertrophy by targeting some translational molecules in the heart, such as eukaryotic initiation factor 4E (Eif4e), Mef2a, Gata4, and histone deacetylase6 (HDAC6) [25-27]. MiRNAs associated with myocardial hypertrophy might be used as a promising therapeutic target [22,23]. Cardiac remodeling following volume or pressure overload of cardiac chambers plays a crucial role in the pathogenesis of CHF. Many investigations have been done to find a potent therapeutic tool to reverse or inhibit further myocardial structural changes in heart disease. MiRNAs have shown some therapeutic advantages by addressing myocardial remodeling and fibrosis. MiRNA-24 has some regulatory effects on myocardial fibrosis in patients suffering from ischemic heart disease [24]. Recent advances in the development of pharmacological inhibitors and activators of miRNAs, such as miR-mimics, antagomiRs, and decoys, made it possible to manipulate the expression level of miRNAs involved in cardiac remodeling and CHF [22]. Looking for miRNAs' dysregulations in occult stage MMVD in dogs may finally lead to an exploration of a new drug to break the degeneration process of mitral leaflets in the early stages of the disease and prevent the occurrence of CHF in affected dogs.

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