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Review

Role of microRNAs in atrial fibrillation: New insights and perspectives

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ABSTRACT

MicroRNAs (miRNAs) are small non-coding RNA molecules that negatively regulate gene expression of their targets at the post-transcriptional levels. They typically affect the mRNA stability or translation finally leading to the repression of target gene expression. Notably, it is thought that miRNAs are crucial for regulating gene expression during heart diseases, such as atrial fibrillation (AF). Numerous studies identify specific miRNA expression profiles associated to different histological features of AF, both in animal models and in patients. Therefore, we review the latest experimental approaches from the perspective of understanding miRNA gene expression regulatory networks in AF. In addition, miRNAs have also emerged as possible therapeutic targets for the treatment of AF. In this review, we discuss the experimental evidence about miRNAs both as potential non-invasive early diagnostic markers and as novel therapeutic targets in AF.

Contents

1. Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, is associated with substantial cardiovascular morbidity and mortality, with stroke being the most critical complication [1–3]. AF causes symptoms such as palpitations, dizziness, breathlessness, and chest pain, and is associated with cardiovascular morbidity and mortality, mainly due to embolic stroke and heart failure (HF) [4–7]. Management of AF

Abbreviations: ECMs, extracellular matrix; TGF-β1, transforming growth factor-β1; MiRNAs, microRNAs; AF, atrial fibrillation; HF, heart failure; RISC, RNA-induced silencing complex; AGO, Argonaute; Cx, connexin; Spry1, sprouty 1; CTGF, connective tissue growth factor; MI, Myocardial infarction; SR, Sinus rhythm.

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patients is focused on reducing symptoms and preventing complications associated with the arrhythmia [8,9]. Usually, two therapeutic approaches are available: a "rhythm control" strategy, terminating AF and maintaining sinus rhythm, and a "rate control" strategy, allowing the patient to remain in AF but controlling the ventricular response [1,10–12]. However, there is no therapy for AF in general, largely because the underlying basis of AF is unclear. A better mechanistic understanding of the molecular basis of AF may allow for the development of safer and more effective treatment approaches.

The mechanisms underlying AF susceptibility are multiple and incompletely understood. The two major determinants of AF maintenance are reentry and ectopic impulse formation [13,14]. The changes in atrial structure and function that result from heart disease, and indeed AF itself, constitute atrial remodeling and are key elements of the AF substrate. In addition, genetic factors establish electrophysiological substrates that determine individual vulnerability to AF occurrence and maintenance [15,16]. Particular emphasis is placed on understanding how altered expression of non-coding RNA transcripts known as miRNAs play a key role in the etiology of AF [17].

MiRNAs are endogenous, small non-coding RNAs which possess a central role in the regulation of both mRNA and protein expression of the target genes [18–20]. The miRNAs act at post-transcriptional level as approximately 22 nucleotides targeting the 3′-untranslated regions (3′-UTRs), which typically contain defined stability elements (including miRNAs binding sites) [21,22]. Specifically, the binding of miRNAs to the complementary sequences of the target mRNAs conveys close to the target the RNA-induced silencing complex (RISC) proteins [23,24]. In summary, the miRNAs exert their specific regulatory functions affecting the stability or translation of targeted mRNA [25–27]. Importantly, there have been described to partake in numerous cellular processes such as proliferation, differentiation, cellular growth, and tissue remodeling, being also implicated in several human pathologies [28–32]. Emerging data suggest that these miRNAs' modifications also impact on the development of AF. Several miRNAs have been described as important regulators of AF [33,34].

This review describes biogenesis, function, activity and regulation of miRNAs with particular concern for their involvement during AF. We also provide an introduction to miRNA modifications as well as an outline of how these changes pertain to the development of AF. Thus, the identification of candidate miRNAs and their target genes implicated in AF and the evaluation of the consequences of mutations in their target sites coupled to gene expression and phenotype studies should improve our understanding of the molecular mechanisms responsible for AF occurrence and development (Fig. 1).

2. The pathogenesis of AF

AF is characterized by rapid irregular atrial activation [35,36]. The most prevalent theory on the mechanism of AF is multiple electrical wavelet re-entry pathways of the atrium [37,38]. A shortening of the atrial action-potential duration and effective refractory period has long been considered a major feature in the multiple wavelet re-entry hypothesis [39]. Atrial electrical remodeling is also thought to play a part in the maintenance of this arrhythmia [36,40]. Atrial electrical conduction is normally influenced by the sympathetic and parasympathetic nerves and can be altered by a variety of acquired diseases, such as ischemic heart disease, fibrosis or hypertrophy [41–46]. Usually, AF may be classified as paroxysmal, persistent or permanent; paroxysmal fibrillation accounts for 35–40% of all atrial fibrillation, however there is a 30–50% chance of paroxysmal atrial fibrillation converting to a permanent state [47,48]. Most atrial fibrillation is associated with cardiac pathology such as hypertension, atherosclerosis, cardiomyopathy or valvular disease. But, the emerging information on the genetic basis for this disease is being elucidated and might offer new hope for therapy and prevention.

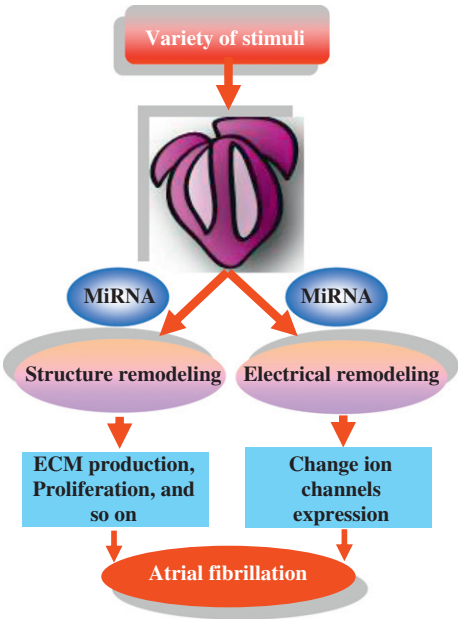

Fig. 1. Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia, it can cause lethal ventricular arrhythmias, palpitations, dizziness, breathlessness, exacerbate heart failure, and constitute a risk factor for ischaemic stroke. The pathogenesis of AF contains electrical and structure remodeling.

3. MiRNA biogenesis and biological function

MiRNAs, are small non-coding RNA species that regulate gene expression at the post-transcriptional level, and first discovered in *Caenorhabditis elegans* [49,50]. Mature miRNA are between 18 and 25 nucleotides (nt) in length and are initially transcribed as primary-miRNA (pri-miRNA) molecules which contain a characteristic stem loop structure [51]. During the canonical miRNA biogenesis pathway the pri-miRNA is processed into pre-miRNA through two ribonuclease (RNase) III-family members that are Drosha and Dicer [52,53]. Drosha binds and cleaves the dsRNA precursor at the stem-loop structure bearing 60–100 nucleotides RNA precursor [54,55]. Drosha, in collaboration with its cofactor DGCR8, and other functional proteins (as p68 and p72 helicases) compose the microprocessor complex [56,57].

Following the first cleavage, which exerted by Drosha into the nucleus, the resulting pre-miRNA moves into the cytoplasm transported by the exportin-5 (Exp5)/Ran-GTP complex [58]. The mature miRNA primarily targets the 3′ UTR of an mRNA strand based on sequence homology [59]. The nucleotides in the 2–7 position of the 5′ end of the mature miRNA, termed the "seed" sequence, are essential for target recognition and binding [60]. Once in the cytoplasm, the pre-miRNA undergoes a second cleavage by the RNase III enzyme Dicer, generating a mature 20–23 nucleotides miRNA: miRNA star duplex [61,62]. The duplex is composed by the guide strand and the passenger strand, which each has a different destiny, since the first is loaded into Argonaute (AGO) complex while the latter is released and degraded [63,64]. Once an mRNA is targeted by a miRNA, its gene expression is down-regulated either by induction of mRNA degradation or blocking of translation by the miRNA, which occurs through conserved mechanisms [65]. Although translation repression by miRNA occurs at the targeted mRNAs through inhibition of translation initiation or elongation, recent studies suggest that mRNA degradation is the primary mechanism by which miRNAs reduce protein output [66,67]. In mammals, the miRNA-mediated gene silencing is guided by an incomplete matching of nucleotides among miRNA and target RNAs resulting in repression of protein synthesis and mRNA deadenylation and consequent degradation [68–70]. Some intronic miRNA precursors, however, bypass Drosha processing to