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Review

MicroRNAs: Emerging biomarkers for atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) causes severe cardiac dysrhythmia among patients with cardiovascular diseases. AF increases the risk of stroke and heart failure and is a growing public health concern. AF is also associated with various disease conditions such as hypertension, coronary artery disease, aging, and diabetes mellitus. The mechanism underlying AF is not completely understood due to its complexity. However, experimental and clinical data have revealed that the prevalence of this disease is associated with atrial arrhythmogenic remodeling. Currently, there are no biomarkers that are available for the early diagnosis of AF. Several studies have proposed microRNAs (miRNAs) as useful biomarkers for the diagnosis of AF due to their stability and easy availability both in atrial tissue and circulating blood. miRNAs play an important role in the development of the heart. The dysregulation of miRNA expression is associated with cardiac remodeling. Genetic factors strongly contribute to the pathogenesis of AF. Recently, single nucleotide polymorphisms (SNPs) in various genes and miRNAs have been reported to be associated with AF. The aim of this review was to discuss the correlation between SNPs in miRNAs and AF, including those miRNAs that are commonly reported as potential biomarkers for AF.

Contents

Introduction

Atrial fibrillation (AF) is the most prevalent sustained type of cardiac arrhythmia. The genetic, molecular, and environmental

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factors that are associated with AF are also the major risk factors for morbidity and mortality among patients with cardiovascular diseases [1]. It is estimated that more than 33 million individuals are suffering from AF worldwide. The incidence of AF among men is 3-fold higher than that among women [2]. Electrocardiography (ECG) is the most commonly used method to diagnose AF. However, the short duration of recording in ECG limits the diagnosis of AF in asymptomatic patients. Hence, there is a need to identify biomarkers for the early diagnosis and treatment of AF [3].

Heart failure, diabetes, arterial hypertension, hyperthyroidism, obesity, sex, and structural and ischemic heart disease are the most common risk factors that are associated with AF. However, more than 20% of AF cases are not associated with these risk factors (lone AF) [4]. The genetic component is a strong risk factor for AF. The individuals with at least one parent with AF are more prone to develop AF than those individuals whose parents do not have any history of fibrillation [5]. Recently, genome-wide association studies (GWAS) and international collaborative meta-analysis have identified various genetic loci that are potentially associated with AF [6].

MicroRNAs (miRNAs) were first discovered in 1993 by Lee et al. in *Caenorhabditis elegans* [7]. The miRNAs are single-stranded, non-protein-coding RNAs consisting of approximately 22 nucleotides. miRNAs are involved in the regulation of post-transcriptional gene expression by binding with the target mRNA at the 3′ UTR (3′ untranslated region) [8]. miRNAs play a vital role in various developmental processes including cell growth, proliferation, differentiation, and metabolism [9]. In the mammalian genome, about 2200 miRNAs have been reported and about one-third of the human genome is regulated by miRNAs [10]. The change in miRNA expression level is reported to be associated with various pathological conditions such as neurological diseases, autoimmune diseases, cardiovascular diseases, and cancer. For example, the change in miRNA expression pattern can transform normal cells into malignant cells [11]. The presence of miRNAs has been reported frequently in circulating blood and cardiac muscles, both in humans and animal models [12,13].

Cardiac remodeling is associated with the change in miRNA expression in cardiac tissues and is reported to be a potential prognostic and diagnostic biomarker [14]. The modulation of miRNA expression is reported to reduce or increase the susceptibility to develop AF in vivo. Hence, miRNAs can be a potential therapeutic agent for the treatment of AF [15].

Biogenesis of circulating miRNAs

The biosynthesis of miRNAs occurs in the nucleus. The miRNA gene clusters are commonly found within the intergenic regions (IRG). In humans, the RNA polymerase-II transcribes the miRNA gene to generate the primary miRNA (pri-miRNA) [16]. The RNA polymerase-III, Drosha, and DGCR8 (DiGeorge Syndrome Critical Region-8) protein cleave the pri-miRNA to generate the precursor miRNA (pre-miRNA), which has a hairpin-like structure [17]. Further, Exportin-5 and Ran-GTP mediate the active transport of the pre-miRNA to the cytoplasm. In the cytoplasm, the pre-miRNA is further processed by the transactivation-responsive RNA-binding protein (TRBP) and the RNase III Dicer protein to generate the miRNA duplex, which is approximately 22 nucleotides long [18]. The Argonaute-2 (AGO2) protein drives the unwinding of miRNA duplex (miR-3p/miR-5p duplex) resulting in two single-stranded miRNAs. The 5′ end of the strand is loaded into the RNA-induced silencing complex (RISC), which is then guided to the 3′ UTR (3′ untranslated region) of mRNA [19] to negatively regulate the mRNA expression [20].

Role of microRNA in the pathophysiology of AF

The miRNAs play a crucial role in the pathophysiology of AF by regulating the atrial remodeling mechanisms. The down-regulation and upregulation of miRNA expression are genetically programmed and contribute to the developmental changes. However, the change in the miRNA expression level in the circulating blood and the tissues is associated with the development of various cardiovascular diseases including AF that lead to myocardial remodeling [21,22]. Various factors such as electrical remodeling [23], structural remodeling [24], autonomic nerve remodeling [25], calcium handling abnormalities [26], inflammation [27], and single nucleotide polymorphisms (SNPs) in miRNA and its related genes are associated with the initiation and maintenance of AF [28] (Fig. 1).

MicroRNA-mediated electrical remodeling in AF

Electrical remodeling is the most common change associated with AF. Electrical remodeling occurs due to the decrease in conductance of L-type Ca^{2+} current (I_{CaL}) and increase in the conductance of inward rectifier current (I_{K1}). The change in the electrical properties of Ca^{2+}-activated K^+ channels and connexin 40 (Cx40), connexin 43 (Cx43) ion channels also trigger the AF-related electrical remodeling [23]. Several miRNAs are involved in the process of electrical remodeling (Table 1 [29–71]).

miRNA-1: miRNA-1 (miR-1) is abundantly expressed in the cardiac muscles and has a role in cardiac development and electrical activity. However, dysregulation in the expression of miR-1 results in serious cardiac conditions such as cardiac arrhythmia, cardiac hypertrophy, and myocyte proliferation. Further, the arrhythmogenic potential of miR-1 is associated with ischemic heart diseases [72]. The plasma miR-1 level in the left atrium appendage (LAA) is higher than that in the pulmonary vein [73]. A study on the rabbit model of atrial tachypacing (A-TP) reported that the overexpression of miR-1 shortens the right atrial tachypacing-induced atrial effective refractory period (AERP) and increases the rectifier potassium current (I_{Ks}) by downregulating the KCNE1 and KCNB2 genes. Further, the downregulation of KCNE1 and KCNB2 genes was inversely proportional to the miR-1 knockdown by the anti-miR-1 inhibitor oligonucleotides. KCNE1 and KCNB2 are the target genes for miR-1. It was suggested that the targeted downregulation of these potassium channel genes amplifies the duration and incidence of AF. The study demonstrated the critical role of miR-1 in the electrical remodeling of AF and the clinical importance of miR-1 as a therapeutic agent for AF [29]. A study on the expression of cardiac muscle-specific miRNAs in the right atrial appendage (RAA) of postoperative AF (POAF) patients revealed that the miR-1 expression is upregulated after coronary artery bypass graft (CABG) surgery and that miR-1 has an important role in the development of POAF and postoperative apoptosis. However, there was no difference in the plasma miR-1 level between the patients with POAF and those with sinus rhythm (SR) or those without AF history [30].

Some studies have reported that the miR-1 expression in aged patients with AF is lower compared to that in young patients with SR. The decreased miR-1 expression results in the upregulation of HCN2/HCN4 genes. This indicated that the miR-1 expression level changes with age [58]. A decreased miR-1 expression, enhanced expression of Kir2.1 and the corresponding increased conductance of I_{K1} were observed in patients with persistent AF. This results in slow cardiac conduction and increases the risk for inducing AF [74]. However, multiple studies support the association between the miR-1 expression level and cardiac arrhythmias. Several studies have demonstrated the miR-1 modulates cardiac electrical remodeling by decreasing the concentration of intracellular

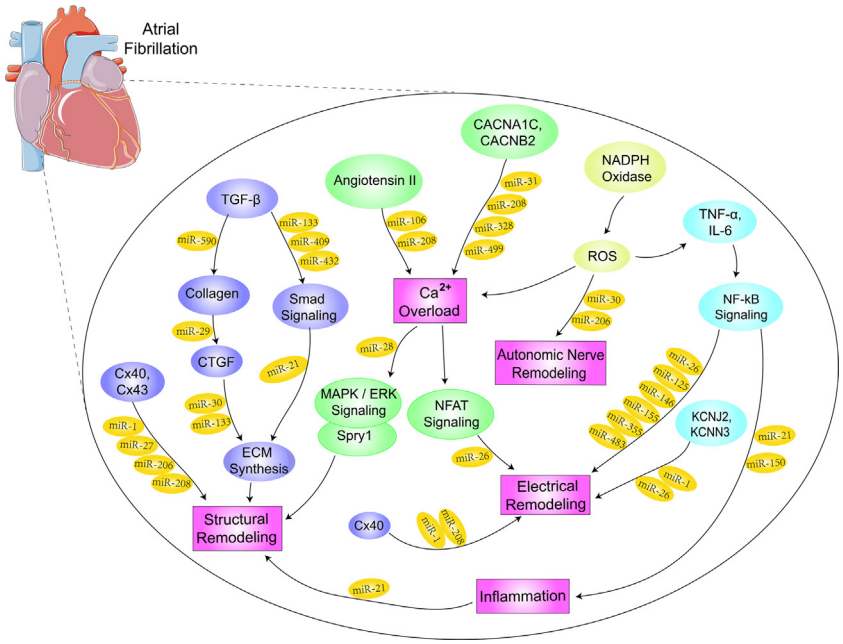

Fig. 1. Atrial fibrillation (AF) mechanisms resulting from atrial remodeling. These mechanisms can be the consequence of other cardiac diseases that promote AF or the consequence of AF itself (AF begets AF). miR, MicroRNA; TGF-β, Transforming Growth Factor-β; CTGF, Connective Tissue Growth Factor; ECM, extracellular matrix; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinases; SMAD, SMAD Family Member; SPRY1, Sprouty RTK Signaling Antagonist 1; CACNA1C, Calcium Voltage-Gated Channel Subunit α 1C; CACNB2, Calcium Voltage-Gated Channel Auxiliary Subunit β2; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; ROS, reactive oxygen species; Cx40, connexin 40; Cx43, connexin 43; TNF, Tumor Necrosis Factor; IL-6, interleukin-6; KCNJ2, Potassium Voltage-Gated Channel Subfamily J member 2; KCNN3, Potassium Calcium-Activated Channel Subfamily N member 3; NF-kB, nuclear factor kappa B subunit; NFAT, Nuclear Factor of Activated T-cells.

Table 1
MicroRNA in association with atrial fibrillation as potential biomarker.

miRNA	Source	Study model	Target gene	Regulatory mechanism	Remodeling mechanism	References
miR-1	Plasma/atrial tissue	Human, rabbit	KCNE1, KCNB2, KCNJ2, HCN2, HCN4	Up (tissue), down (blood)	Electrical/structural	[29–31]
miR-21	Atrial tissue plasma	Human, rat, mice	CACNA1C, CACNB2, SPRY1, PTEN, STAT3, Smad7, WWP-1	Up (tissue), down (blood)	Electrical/structural	[32–35]
miR-26	Atrial tissue	Human, mice, dog	Kir2.1, KCNJ2	Down	Electrical/structural	[36,37]
miR-30	Atrial tissue	Rabbit, rat, dog, human	I_{KACh}, snail 1	Down	Electrical/structural	[38–40]
miR-31	Atrial tissue	Human, goat, mice	nNOS, Kir3.1, Cav1.2	Up	Electrical	[41]
miR-106	Atrial tissue plasma	Human, mice	RYR2, klf2a	Down	Electrical	[42]
miR-208	Plasma	Human, mice	CACNA1C, CACNB2, MYH7, Cx40	Up	Electrical/structural	[43,44]
miR-328	Plasma	Human, mice, dog	CACNA1C, CACNB1	Up	Electrical	[45,46]
miR-499	Atrial tissue	Human, mouse	KCNN3, CACNB2	Up	Electrical	[47,48]
miR-27	Atrial tissue	Mice	ALK5, Cx40	Up	Structural	[49,50]
miR-28	Atrial tissue	Rat	ERK signaling pathway	Up	Structural	[51]
miR-29	Plasma/atrial tissue	Human, dog, mice	FBN, COL1A1, COL3A1	Down	Structural	[34,52]
miR-34	Atrial tissue	Human	Ank-B	Up	Structural	[53,54]
miR-125	Atrial tissue	Human	IL-6R, TNFα	Down	Structural	[55]
miR-126	Serum	Human, mice	EGFL7	Down	Structural	[56,57]
miR-133	Atrial tissue	Human, rat, dog, mice	KCNH2, KCNQ1, HCN2, HCN4, TGF-β1	Down	Structural	[30,58–62]
miR-146	Atrial tissue	Human, mice	TIMP-4	Up	Structural	[63]
miR-150	Plasma, serum	Human	IL-6, IL-18, TNF-α/β	Down	Structural	[57,64]
miR-199	Atrial tissue	Human	SIRT1	Down	Structural	[65]
miR-206	Atrial tissue	Mice, dog	SOD1, GCH1, Cx43	Up	Structural	[25,66,67]
miR-483	Plasma	Human	IGF2	Up	Structural	[68]
miR-590	Atrial tissue	Human, dog	TGF-β1, TGF-β R2	Down	Structural	[62,69]
miR-155 miR-24	Atrial tissue	Human, pig	eNOS	Up	Structural	[70]
miR-409 miR-432	Plasma	Human	SMAD2, ITGB3, ACE, CDKN2B	Down	Structural	[71]

Studies show the presence of specific miRNAs in atrial fibrillation and their up and down regulation both in circulating blood and atrial tissue. *Abbreviations*: CACNA1C, Calcium Voltage-Gated Channel Subunit α 1C; CACNB2, Calcium Voltage-Gated Channel Auxiliary Subunit β2; SPRY1, Sprouty Homolog 1 RTK Signaling Antagonist-1; PTEN, Phosphatase and Tensin Homolog; STAT3, Signal Transducer and Activator of Transcription-3; KCNH2, Potassium Voltage-Gated Channel Subfamily H Member-2; IL, interleukin; TNF, Tumor Necrosis Factor; KCNQ1, Potassium Voltage-Gated Channel Subfamily Q Member-1; HCN, Hyperpolarization Activated Cyclic Nucleotide Gated Potassium and Sodium Channel; Kir2.1, Inward Rectifier Potassium Channel-2; TGF-β1, Transforming Growth Factor-β1; TGF-βR2, Transforming Growth Factor β Receptor-2; SOX, SRY-Box; eNOS, endothelial nitric oxide synthase; SOD1, Superoxide Dismutase 1; RYR2, ryanodine receptor 2.

calcium ions that eventually reduce the CACNB2 expression [75]. Additionally, the negative regulation of Ca^{2+} handling proteins, such as calmodulin, protein phosphatase 2A (PP2A), Na^{+}/Ca^{2+} exchanger (NCX), and phospholamban contribute to the pathogenesis of AF by shortening refractoriness [31]. Further, the inhibition of miR-1 has cardioprotective effects as the miR-1 inhibition targets the Bcl-2 gene and reduces the number of apoptotic cardiomyocytes [76].

miRNA-328: miR-328 promotes atrial remodeling. A study revealed that the upregulation of miR-328 in circulating blood increases the prevalence of AF and plays an important role in calcium handling and electrical remodeling of cardiomyocytes. The upregulation of miR-328 decreases the gene expression of CACNA1C and CACNB1 both in human and canine models. Consequently, the I_{CaL} reduces the L-type calcium channel activity and shortens the action potential duration (APD), which augments the AF vulnerability [45,77]. The expression of miR-328 in the LAA was reported to be higher compared to that in the peripheral and pulmonary vein blood of patients with AF, which was not observed in the control subjects. Hence, it was hypothesized that the localized expression of miR-328 in the left atrium may be involved in the cardiac remodeling of patients with AF [46].

miRNA-499: A comparative study on patients with permanent AF and those with normal SR revealed that the upregulation of miR-499 markedly downregulates the expression of cardiac SK3 (small conductance calcium-activated potassium channel 3) by targeting the KCNN3 gene [47]. Further, the miR-499 was reported to be upregulated during the remodeling of L-type calcium currents by targeting CACNB2 in patients with AF [48]. The miR-499 expression in patients with rapid AF rhythm was 2.3-fold higher compared to that in patients with slow AF rhythm and in control group patients [78].

MicroRNA-mediated structural remodeling in AF

The miRNAs that are involved in the structural remodeling regulate the genes that encode proteins responsible for the formation of extracellular matrix (ECM) and promote atrial fibrosis by initiating antifibrotic signaling pathways [24]. These miRNAs are predominantly involved in decreasing the conduction velocity and increasing the reentrant activity interval [79], and Table 1 contains some miRNAs related to structural remodeling [29–71].

miRNA-21: miR-21 was reported to upregulated in the cardiomyocytes of patients with chronic AF. This results in the downregulation of two voltage-gated calcium channel (VGCC) subunits, CACNA1C (1αC) and CACNB2 (β2) that leads to the reduction in I_{CaL} [32]. The upregulation of miR-21 in fibroblast increases the risk of cardiac fibrosis and the associated AF. The enhanced expression of miR-21 in the rat model and in the left atrium of patients with AF downregulated the expression of Sprouty-1 (SPRY1) target by augmenting the mitogen-activated protein kinase/extracellular signal-regulated kinases (MAPK/ERK) signaling pathway to promote atrial remodeling and fibrosis [80]. However, in vivo administration of antagomir-21 (anti-miR-21) potentially reduces the atrial fibrosis and AF by silencing the miR-21 activity [33]. The upregulation of miR-21 promotes atrial remodeling in the rat model by activating the PI3K signaling pathway, which results in the inhibition of PTEN gene expression. Hence, downregulating the miR-21-related signaling pathways can be a novel therapeutic approach for AF [81].

miRNA-29: miR-29b plays a critical role in the remodeling of ECM protein [52] by targeting the COL1A1 (collagen-1A1), COL3A1 (collagen-3A1), and fibrillin genes. The plasma level of miR-29b in patients with AF (approximately 54% reduction) and in patients with both congestive heart failure (CHF) and AF (approximately 84% reduction) is substantially lower than that in the control group. Further, the miR-29b expression in the atrium reduces by approximately 54% compared to that during SR in patients with chronic AF. In mice, the adeno-associated virus-mediated down-regulation of miR-29b markedly increases the atrial COL1A1 mRNA expression and collagen content in the cardiac tissue. This indicates the potential role of miR-29 in atrial fibrotic remodeling. Hence, miR-29 can be a potential biomarker and a therapeutic target [34].

miRNA-126: miR-126 is derived from the EGFL7 gene and is abundantly expressed in the human heart. Further, miR-126 has an active role in angiogenesis [56]. The miR-126 level in patients with AF is markedly lower than that in the control subjects. Additionally, the miR-126 level in patients with heart failure (HF) and AF is drastically lower than that in patients with either HF or AF. Additionally, the level of N-terminal prohormone brain natriuretic peptide (NT-proBNP) in patients with AF was lower than that in patients with HF or patients with HF and AF. This indicates the correlation between the serum miR-126 level and the severity of the disease [57].

miRNA-150: miR-150 plays a major role in the pathogenesis of AF. The expression of miR-150 was low in the platelets and serum of patients with chronic systolic heart failure with or without AF. The expression level of miR-150 in the platelets of patients with AF is reduced by approximately 3.2-fold compared to that in the platelets of control subjects. Similarly, the serum miR-150 level in patients with AF is 1.5-fold lower than that in patients with HF and without AF. This indicates a strong correlation between the lower serum and platelet levels of miR-150 and AF. Furthermore, it was speculated that the lower level of miR-150 may interfere with various pathways that are involved in AF including atrial remodeling, inflammation, platelets function, platelets aggression, and fibrosis [82].

In a prospective study, the expression level of miR-150 was measured in plasma and atrial tissue of patients with and without AF and of patients undergoing cardiac ablation. The plasma miR-150 level in patients with AF was 2-fold lower than that in the control subjects. Further, the plasma miR-150 level among patients with paroxysmal atrial fibrillation was lower when compared to that in patients with persistent AF. However, the expression level of miR-150 one-month post-AF ablation was 3-fold higher than that before AF ablation. This indicates that the higher expression of circulating miR-150 has beneficial effects [64].

miRNA-483: The circulating miR-483-5p in patients with POAF can be a potential biomarker for early prediction of AF. miR-483-5p is transcribed by the IGF2 gene. The upregulation of IGF2 results in miR-483 overexpression, which consequently enhances the expression of pro-inflammatory mediators by regulating the interleukin-6 (IL-6) and nuclear factor kappa-B (NF-kB)-mediated pathways. The serum miR-483-5p level in pre-operative patients was high. Additionally, surgery can trigger AF in patients with POAF [68]. This suggests that miR-483 can be a potential biomarker.

miRNA-155 and miRNA-24: The upregulation of both miR-155 and miR-24 was reported in the swine model and human blood sample of patients with AF, which was due to the regulation of eNOS expression and nitric oxide (NO) production. The study further demonstrated the miR-155 and miR-24 are downregulated in patients with AF post-ablation and in the animal model compared to those who have not undergone catheter ablation (pre-ablation). The decreased expression of miR-155 and miR-24 was associated with the reduction in the NO level. Hence, this validates the role of miRNAs in AF, which involves the regulation of the endothelial nitric oxide synthase (eNOS) signaling pathway [70].

miRNA-409/miRNA-432: Both miR-409-3p and miR-432 are downregulated in the plasma of patients with AF. miR-409-3p/miR-432 are known to interact with various signaling molecules such as TGF-β signaling molecules, gap junction channels, ECM

receptors, renin–angiotensin system, and MAPK signaling molecules. The expression of miR-409-3p and miR-432 varies in healthy individuals and in patients with AF before and after catheter ablation. Hence, miR-409-3p and miR-432 can be the biomarkers for AF [71].

MicroRNA-mediated autonomic nerve remodeling in AF

Recent studies have evaluated the role of miRNAs in the initiation and maintenance of AF by neural remodeling. The change in cardiac electrical activity is closely associated with vagal nerve stimulation and with the change in acetylcholine release. These changes result in shortening of APD (action potential duration) and contribute to the progression of AF [83].

miRNA-30: Dysregulation of the cardiac autonomic nervous system plays a fundamental role in the initiation and maintenance of AF by increasing the G-protein gated potassium channel current (I_{KACh}), which shortens the APD [84]. The upregulation of miR-30d is associated with the downregulation of acetylcholine-dependent potassium current (I_{K+}) in patients with persistent AF [85].

miRNA-206: The upregulation of miR-206 promotes the autonomic nerve remodeling by directly targeting the expression of SOD1, which increases the production of ROS (reactive oxygen species) and shortens the AERP. The expression of miR-206 in the lenti-miR-206-infected dogs was reported to be 6-fold higher compared to that in the lenti-anti-miR-206-infected dogs. The study confirmed the correlation between ROS overproduction and AF vulnerability [66]. The downregulation of miR-206 by targeting the GCH1 in the canine model was reported to exaggerate the autonomic nerve remodeling and inhibit the expression of AERP via tetrahydrobiopterin (BH4) pathway, which in turn increases the AF susceptibility [25].

MicroRNA-mediated Ca^{2+} handling abnormality in AF

The change in cardiac miRNA expression affects the calcium handling in cardiomyocytes and contributes to the pathophysiology of various cardiac diseases including ventricular arrhythmogenesis and AF [86]. The intracellular Ca^{2+} imbalance and high atrial rate during AF increases the Ca^{2+} overload and promotes AF by delayed afterdepolarization (DAD). The DAD results from enhanced diastolic Ca^{2+} release from the sarcoplasmic reticulum via ryanodine receptor 2 (RYR2) and promotes the increased Ca^{2+} extrusion through the NCX. Hence, the abnormalities in the intracellular Ca^{2+} homeostasis are also involved in cardiac remodeling [87].

miRNA-106b-25: The downregulation of miR-106b-25 cluster by upregulating the protein expression of RYR2 was observed in patients with persistent AF. Further, the miR-106b-25 knockout mice exhibited a spontaneous increase in Ca^{2+} release through RYR2, which contributes to the AF vulnerability [42].

miRNA-208: Sarcoplasmic reticulum Ca^{2+} adenosine triphosphates type 2a (SERCA2a) regulates the Ca^{2+} concentration by transporting the Ca^{2+} from the cytosol to sarcoplasmic reticulum. The upregulation of miR-208b plays an important role in abnormal Ca^{2+} handling by downregulating SERCA2 protein expression in patients with chronic AF compared to those with SR [44].

MicroRNA-mediated regulation of inflammatory mediators in AF

Several studies have revealed the mechanistic role of inflammatory mediators in the pathophysiology of AF. The blood serum levels of inflammatory biomarkers (C-reactive protein, interleukins, TNF-α, TGF-β, and MCP-1) were reported to be higher in patients with AF as compared to that in patients without AF [88]. Cardiac inflammation and the presence of inflammatory mediators in the general circulation can be used to predict the onset and recurrence of AF [27].

miRNA-21: The upregulation of miR-21 promotes AF and AF susceptibility through STAT3 phosphorylation or through inhibition of TGF-β pathway and by downregulating Smad7. However, in vivo inhibition of miR-21 using anti-miR-21 reduces both AF and fibrosis in the animal model [89,90].

miRNA-150: The secretion of cytokines, such as TNF-α, TGF-β, IL-6, and IL-18 from macrophages and monocytes in response to inflammatory stimuli increases the plasma CRP production in patients with AF when compared to that in the healthy individuals. The C-reactive protein (CRP) plays an important role in systemic inflammation. A strong correlation has been reported between miR-150 and CRP level. The downregulation of miR-150 promotes AF by targeting the genes that are involved in inflammation, which can be a predictive biomarker of AF [13].

SNPs of miRNA and atrial fibrillation

Single nucleotide polymorphism (SNP) is not only associated with phenotypic differences in humans but is also responsible for a wide range of genetically inherited diseases. SNP is the substitution of one nucleotide by another. In miR-499 polymorphism (rs3746444), A–U pair change to G–U in mature miRNA [91]. Several studies have suggested that the miRNA expression varies between healthy and disease conditions. SNP can be introduced at any stage of miRNA biosynthesis including, pri-miRNA, pre-miRNA, target sites (3′ UTR of mRNA), and in the seed region of miRNA, which not only alters the structure and expression of miRNA but is also associated with the progression and prognosis of various diseases including neurological disorders, cancer, gastric mucosal atrophy, type II diabetes and, cardiovascular disease including cardiac arrhythmias [54,92]. Polymorphism in genes encoding atrial natriuretic peptide (ANP), cardiac ion channels (Ca^{2+}, K^{+}, Na^{+}), nucleoporins, and gap junction proteins was reported in patients with AF [93]. More than two hundred SNPs and mutations in primary, precursor, and mature miRNA are reported and most of them are correlated with various human diseases.

However, few studies proposed that the polymorphism in proteins that are involved in the biogenesis of miRNA such as Drosha, DGCR8, Exportin-5, Ran-GTP, AGO2 including the proteins of the miRNA-RISC complex can also alter the overall expression of these proteins and deregulate the mature miRNA expression and function [94].

miRNA-125: Recently, a study demonstrated the role of miR-125a in the development of AF by targeting the interleukin-6 receptor (IL-6R) gene. The study demonstrated that the miR-125 expression is downregulated post-catheter ablation, which promotes AF recurrence. Further, the rs12976445 SNP of miR-125a was reported to affect the normal functioning of mature miRNA by altering the processing of pri-miRNA into pre-miRNA. Furthermore, miR-125a also contributed to the downregulation of miR-125 in patients with AF [55].

miRNA-196: The pre-miR-196a2 polymorphism, rs11614913 alters the mature miR-196a2 expression and its binding to the target mRNA. The individuals with CC + TC genotype ("C" carrier) had an increased risk of developing AF by up to 3-fold compared to the individuals with TT genotype [95].

MicroRNAs as the biomarker for cardiovascular diseases

The expression of miRNA in the tissue and blood can be used as a biomarker for various diseases. According to the National Institute of Health (NIH) and the World Health Organization (WHO), a biomarker is a biological molecule or its products that can be measured in the blood, tissues, or other body fluids as an

indicator of normal and abnormal body function, or that can predict the incidence of disease. Currently, there are no suitable biomarkers for the primary diagnosis of AF. However, the circulating natriuretic peptides or troponins are used as a biomarker for other cardiovascular diseases. The high stability, sensitivity, specificity, and prognostic properties of the circulating miRNAs make them an attractive biomarker for the early diagnosis of numerous diseases [96]. After the discovery of miRNA expression in blood, miRNA expression was also reported in the serum, plasma, erythrocytes, nucleated blood cells, and platelets. The miRNAs in plasma are very stable under extreme conditions such as boiling, altered pH, high or low temperature, and can withstand multiple freeze–thaw cycles and room temperature. The miRNAs can be easily detected with high specificity and sensitivity in the serum and plasma [97]. As the miRNAs are bound to high-density lipoprotein (HDL) or are incorporated within the micro-vesicles, exosomes, and apoptotic bodies, they are resistant to RNase activity. However, the exogenous miRNAs are quickly degraded by the RNase in plasma. The stability of circulating miRNAs and the ease of accessibility in plasma and serum make it a suitable clinical biomarker for several cardiac diseases, including coronary artery disease, AF, acute myocardial infarction, hypertension, and heart failure [59,98].

Several studies have demonstrated that the cardiac-specific miRNAs may be the potential diagnostic biomarker for various cardiac diseases. The miRNAs contribute to the regulation of a number of genes that are involved in the development of AF [64]. Hence, miRNAs can be a new class of diagnostic, prognostic, and predictive biomarkers for AF.

Future directions, limitations, and clinical perspective

AF is associated with a change in miRNA expression level, which can be quantified. Several studies strongly support the correlation between miRNA expression and AF. However, the differential miRNA expression level observed in blood and tissue as well as in the left and right atria may be related to the severity and type of cardiac disease. Additionally, the differential expression of miRNAs is related to the type and phase of AF. Hence, the miRNA expression must be carefully evaluated considering all these factors and the methodology to analyze miRNA must be improved for clinical applications.

Conclusion

The stability and the ease of availability of miRNAs in biofluids including blood make them a promising diagnostic biomarker for various cardiovascular diseases. However, further studies are needed to evaluate the reliable circulating miRNAs as a biomarker for AF. The early detection of miRNA polymorphism or SNP can also improve the diagnosis and, management in patients with AF. Additionally, miRNA polymorphism can be used in the field of personalized medicine. Despite variations in the miRNA expression between various studies, they can be used to understand the underlying mechanism of AF and to evaluate the role of miRNA as a potential biomarker. Additionally, miRNAs can be used for the development of advanced miRNA-based therapies.

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Conflict of interest

The authors declare that there is no conflict of interest.

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