Review Article

A narrative review of non-coding RNAs in atrial fibrillation: potential therapeutic targets and molecular mechanisms

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Objective: This review summarizes the advances in the study of ncRNAs and atrial remodeling mechanisms to explore potential therapeutic targets and strategies for AF.

Background: Atrial fibrillation (AF) is one of the most common arrhythmias, and its morbidity and mortality rates are gradually increasing. Non-coding ribonucleic acid RNAs (ncRNAs) are transcribed from the genome and do not have the ability to be translated into proteins. A growing body of evidence has shown ncRNAs are extensively involved in the pathophysiological processes underlying AF. However, the precise molecular mechanisms of these associations have not been fully elucidated. Atrial remodeling plays a key role in the occurrence and development of AF, and includes electrical remodeling, structural remodeling, and autonomic nerve remodeling. Research has shown that ncRNA expression is altered in the plasma and tissues of AF patients that mediate cardiac excitation and arrhythmia, and is closely related to atrial remodeling.

Methods: Literatures about ncRNAs and atrial fibrillation were extensively reviewed to discuss and analyze.

Conclusions: The biology of ncRNAs represents a relatively new field of research and is still in an emerging stage. Recent studies have laid a foundation for understanding the molecular mechanisms of AF, future studies aimed at identifying how ncRNAs act on atrial fibrillation to provide potentially promising therapeutic targets for the treatment of atrial fibrillation.

Keywords: Atrial fibrillation (AF); non-coding RNA (ncRNA); microRNAs (miRNAs); atrial remodeling; molecular mechanisms

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Introduction

Non-coding RNAs (ncRNAs) do not encode proteins, and include transfer RNAs (tRNAs), small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). The common features among these RNAs are that they can be transcribed from the genome but are not translated into proteins, and can perform their respective biological functions at the RNA level. NcRNAs play a key role in the physiology and normal development of the cardiovascular system, but have also been implicated in the development of cardiovascular diseases (1).

Atrial fibrillation (AF) is common type of arrhythmia that arises due to serious disorder in the atrial electrical activity (2). It is induced by rapid and disordered AF that replaces regular physiological atrial electrical activity. AF shares strong links with other cardiovascular diseases,

such as coronary artery disease, valvular heart disease, and hypertension (3), which are referred to as upstream risk factors. The association between comorbid cardiovascular disease and AF is complex and not completely understood; the accurate mechanism by which cardiovascular risk factors induce AF is not fully understood either and is currently being investigated. Catecholamine excess, hemodynamic stress, atrial ischemia, atrial inflammation, metabolic stress, and neurohumoral cascade activation may promote AF.

To date, there have been several proposed hypotheses regarding the mechanism of AF, including the multiple wavelet and automatic focus hypotheses (4). The focal origin of AF is supported by several experimental models, indicating that AF persists only in isolated regions of atrial myocardium, and the pulmonary veins appear to be the most frequent source of these automatic foci (5). The multiple wavelet hypothesis proposes that fractionation of wave fronts propagating through the atria results in self-perpetuating "daughter wavelets". In this model, the number of wavelets is determined by the refractory period, conduction velocity, and mass of atrial tissue. Increased atrial mass, shortened atrial refractory period, and delayed intra-atrial conduction increase the number of wavelets and promote sustained AF (6). One study reported on the complex relationship between trigger and trigger-substrate substrates in patients with AF, and suggested an initiating mechanism for the occurrence of AF (7). The onset and maintenance of paroxysmal AF is associated with ectopic activity; consistency within and between patients in trigger-substrate interaction during the development of AF has also been reported (7).

Following the occurrence of AF, the loss of effective atrial contraction and diastole due to the rapid and disordered rhythm, combined with the disordered ventricular rate caused by decremental conduction of the atrioventricular node in response to rapid atrial excitation, often leads to impaired cardiac function and atrial appendage thrombosis (2). With the increasing aging population, the incidence of AF has gradually increased, leading to significant research advances for understanding its mechanisms, diagnosis, and treatment. In recent years, with the increase and depth of ncRNA research, it might be regarded as a biomarker of atrial fibrillation (8,9). This review set out to describe some of the more recent developments on ncRNAs in AF to develop a better and comprehensive understanding of the interaction between them and explore potential therapeutic targets and strategies for AF, which will likely lead to a more translational approach for preventing and treating AF. We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4483).

miRNAs in AF

Changes to miRNA levels in patients with AF

Previous studies have reported changes in the transcription levels of miRNAs in patients with AF. Due to the large heterogeneity in the design of previous studies, we focused on studies in which the control group was a healthy population.

In circulation, increased expression of *miR-9*, *miR-152*, *miR-374a*, *miR-454*, and *miR-664* has been observed in patients with AF (10,11). One study that screened patient plasma samples revealed that the concentration of *miR-150* in patients with paroxysmal or persistent AF was significantly lower than that in a control group with normal cardiac rhythm (4), which was also observed in two additional studies (12,13). Reduced plasma levels of *miR-29b* have also been observed in AF patients with or without congestive heart failure (14). Another study that included healthy controls, well-controlled AF patients, and acute new-onset AF patients showed increased expression of *miR-133b*, *miR-328*, and *miR-499* in patients with acute new-onset AF compared to the healthy controls, as well as decreased expression of *miR-21* in patients with well-controlled AF (15). However, a large cohort study subsequently contradicted this, and found that levels of *miR-328* were lower in patients with AF after adjusting for confounding factors (16). This discrepancy reflects the complex regulation of miRNA expression, as well as the temporal variation in circulating miRNA levels in AF patients. Moreover, recent studies have also shown significant elevation of *miR-223-3p* and *miR-320a-3p* in patients with AF (17,18).

Various differentially expressed miRNAs have also been identified at the tissue level. In these analyses, samples were mostly obtained from atrial tissue in coronary artery bypass grafting (CABG) or valve replacement, and control groups were comprised of patients who did not have AF but had coronary or valvular disease. A study on myocardium-specific miRNA expression in the right atrial appendage of patients with postoperative AF showed upregulation of *miR-1* expression after CABG (19). Although other continuous studies screened a range of miRNAs that were differentially expressed in the atrial tissue of patients with AF and sinus

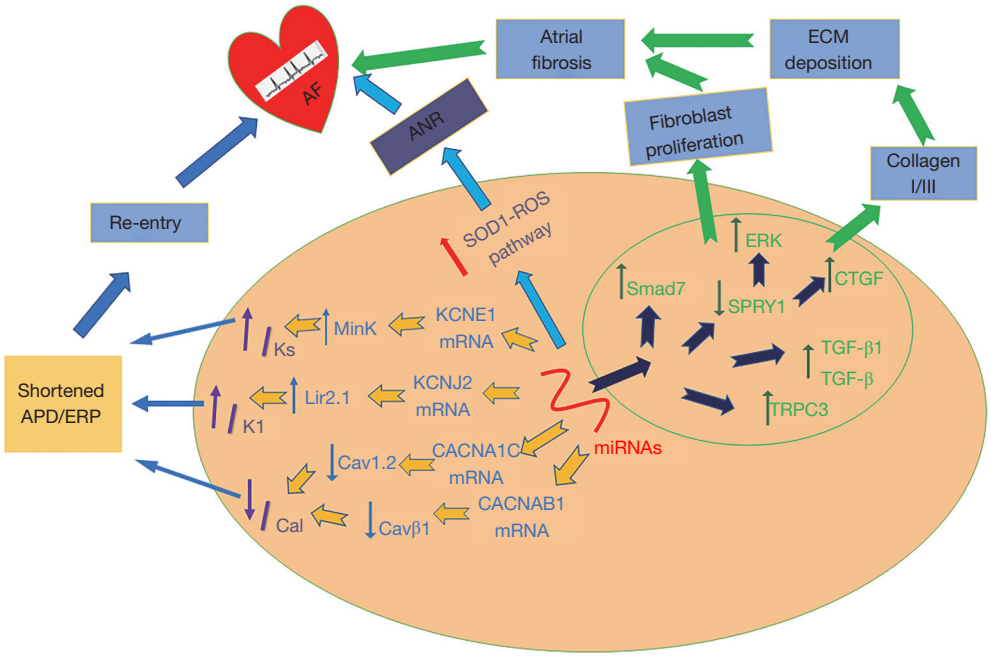

Figure 1 miRNAs in the remodeling of atrial fibrillation. miRNAs, microRNAs.

rhythm, the miRNA most consistently upregulated in these studies was *miR-21*, while *miR-26* and *miR-29* were consistently found to be downregulated (20-23). Notably, some studies have compared miRNA expression levels between different atrial tissues and found that the left and right atria are both affected by the development of AF. However, in patients with normal rhythm or AF, miRNAs may also be differentially expressed between the left and right atria (24-27).

The role of miRNAs in the mechanism of AF

Although the mechanism of AF has not been fully elucidated, the occurrence and development of AF are closely related to atrial remodeling, which mainly includes electrical remodeling, structural remodeling, and autonomic nerve remodeling (ANR).

Electrical remodeling is associated with intercellular ion channels, including potassium (K^+), calcium (Ca^{2+}), and sodium (Na^{2+}) channels. Potassium channel-related miRNAs include *miR-26*, *miR-1*, *miR-30d*, and *miR-499*, which can shorten the action potential duration (APD) and atrial effective refractory period (AERP) by upregulating the atrial slow delayed rectifier potassium current (I_{Ks}) and enhancing the inward rectifier potassium current (I_{K1}) (28). Calcium channel-related miRNAs include *miR-328*, *miR-208a/b*, *miR-21*, and *miR-106b-25* clusters, which can weaken the L-type calcium current (LTCC) and hyperphosphorylate ryanodine receptor type 2 (RyR2), causing Ca^{2+} leakage during diastole (29). At present, *miR-192-5p* is the only miRNA reported to be associated with sodium channel remodeling (30). Structural remodeling is characterized by atrial dilatation and fibrosis. In this process, there is a vicious cycle in which dilated and fibrotic atria induce AF, which can in turn promote atrial dilatation and fibrosis (31,32). Multiple miRNAs are involved in structural remodeling by promoting the deposition of extracellular matrix (ECM) and increasing collagen I/III (33). Similarly, dysregulation of the autonomic nervous system plays an important role in the onset and maintenance of AF (34). The mechanism underlying the roles of miRNAs in atrial remodeling is shown in *Figure 1*.

Electrical remodeling of AF

MiR-1 is the most abundantly expressed miRNA in the myocardium and plays an important role in promoting the occurrence and development of AF. In a rabbit model of AF with rapid atrial pacing, the expression of *miR-1* was significantly increased, whereas *KCNE1* and *KCNB2* were downregulated at both the messenger RNA (mRNA) and protein expression levels. Meanwhile, I_{Ks} was significantly enhanced, and APD and AERP were shortened, promoting

the occurrence of AF (35). Furthermore, analysis using luciferase revealed that *KCNE1* and *KCNB2* were direct targets of *miR-1*, and downregulation of *miR-1* prevented downregulation of *KCNE1* and *KCNB2*, thereby reducing the susceptibility and occurrence of AF (36).

Research on the changes in *miR-1* expression in humans has produced contradicting results. Biliczki *et al.* observed downregulation of *miR-1* and increased I_{k1} in the atrial tissue of patients with AF (37). Downregulation of *miR-1* has also been observed in patients with AF in other studies (19,37). Based on these studies, we speculated that downregulation of *miR-1* regulates *KCNJ2*, thus enhancing I_{k1} in patients with AF. However, the mechanistic role of *miR-1* in AF is likely complex, as both upregulation and unaltered expression of *miR-1* have been observed in studies of human AF (23,29,38). Terentyev *et al.* not only observed increased *miR-1* in human AF but also found that cellular Ca^{2+} influx was increased as a result of enhanced LTCC. The sarcoplasmic reticulum Ca^{2+} channel RyR2 is hyperphosphorylated and activated by calmodulin-dependent protein kinase II (CaMKII) (39). However, studies on *miR-1* and Ca^{2+} dynamics in patients with AF have also been contradictory.

Shan *et al.* found that when *miR-1* was overexpressed, Ca^{2+} influx in atrial myocytes increased, leading to AF (40), while another study found that *miR-1* was downregulated in AF patients, which suppressed the expression of the Cavbeta2 subunit of the LTCC. Ultimately, a reduction in the intracellular Ca^{2+} concentration inhibits the occurrence of AF (13). Feng *et al.* found that *miR-1* was upregulated and the connexin Adam O protein was downregulated, which suppressed the expression of myofibrils; thus, intercellular electrical conduction was slowed, thereby increasing susceptibility to AF (41).

Downregulation of *miR-26* in the atrial tissue of AF patients is associated with an increase in *KCNJ2* and potassium channel 2.1 (Kir2.1) (28). Inhibition of *miR-26a* in mice was found to enhance I_{K1} and increase the occurrence of AF, whereas the overexpression of *miR-26a* reversed this trend in humans (28). Qi *et al.* knocked out *miR-26a in vitro* with locked nucleic acid (LNC)-based drugs in canine fibroblasts to induce an increase in I_{K1}, thereby hyperpolarizing the resting membrane potential (RMP) and enhancing fibroblast proliferation, which was consistent with the above conclusion (42). In addition, a study based on patients with AF and canine models found that *miR-26* acted on *KCNJ2* to activate T cell nuclear factor and increase K^+ influx, thereby shortening APD and causing AF (43). Similarly, Harada *et al.* found that *miR-26a* was downregulated in canine and rat models of AF, and transient receptor potential channel 3 (TRPC3) protein increased (33).

Increased expression of *miR-328* has been reported in both AF patients and animal models; the target genes of *miR-328* are *CACNA1C* and *CACNB1*, which encode the cardiac LTCC subunits Cav1.2 and Cavβ1, respectively (29). In atrial myocytes, *miR-328* targets the genes encoding L-type Ca^{2+} channel proteins to decrease L-type calcium channel (I_{CaL}) density and shorten APD and AERP, thereby enhancing the sensitivity of AF. Conversely, downregulation of *miR-328* by gene knockout can reduce its sensitivity (29). Karnabi *et al.* found that when only the α1 subunit of LTCC was knocked out, *miR-328* was overexpressed and AF did not develop, suggesting that *miR-328* is involved in the development of AF by regulating LTCC (44). Furthermore, a study by Guo *et al.* showed that *miR-328* targeted the 3' non-coding region of the LTCCα1 sequence region, thereby exerting a negative regulatory effect on LTCC and participating in the development of AF (45). Li *et al.* also found that when *miR-328* was overexpressed, the expression of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) decreased and intracellular Ca^{2+} influx increased, suggesting that *miR-328* could regulate intracellular calcium dynamics through the sarcoplasmic reticulum (46).

Structural remodeling of AF

The structural remodeling of AF is characterized by atrial enlargement and fibrosis, of which the latter is considered a hallmark of the pathological process. Fibrosis can promote the maintenance of re-entry, which plays a key role in the development of AF (47,48). MiRNAs participate in structural remodeling during AF, and *miR-21* has been intensively investigated in various studies. *MiR-21* could increase the deposition of ECM and enhance the expression of collagen I and III to promote fibrosis, and several regulatory mechanisms have been proposed. One study found that *miR-21* could target and suppress the expression of *SPRY1*, which is associated with the negative regulation of the extracellular signal-regulated protein kinase (ERK) signaling pathway. Thus, the expression of connective tissue growth factor (*CTGF*) was enhanced, while fibroblasts caused fibrosis. Furthermore, knocking out *miR-21* inhibited fibrosis and decreased the occurrence of AF *in vivo* (49). Another signaling pathway associated with the role of *miR-21* in AF was reported by He *et al.*, who found that *miR-21* could repress the expression of *Smad7*,

which was associated with an increase in collagen I and III. Inhibition of *miR-21* upregulates *Smad7* and suppresses atrial fibrosis (50). *MiR-21* can also promote atrial fibrosis via an inflammation-related pathway. Downregulation of *miR-21* in rats with pericarditis and AF could suppress the phosphorylation of transcription activator 3 (*STAT3*), thereby downregulating the expression of fibrosis-related genes and reducing the susceptibility to AF (51,52).

Previous studies have shown that *miR-133* and *miR-590* are associated with AF via multiple mechanisms. Nicotine has been shown to significantly downregulate *miR-133* and *miR-590* and enhance the expression of *TGF-β1* and *TGF-β receptor II* genes. An *in vitro* experiment showed that transfection of *miRNA-133* and *miRNA-590* into cultured atrial fibroblasts could reduce the expression of collagen, and that *TGF-β1* and *TGF-β receptor II* were also downregulated (53).

MiR-1 is not only involved in atrial electrical remodeling but also in the structural remodeling of AF. Karakikes *et al.* found that exogenous *miR-1* intervention could reverse cardiac hypertrophy and fibrosis caused by pressure loads. With the upregulation of *miR-1*, the mRNA expression of *Fbln-2* was downregulated, and myocardial fibrosis was suppressed by inhibiting the increase in ECM deposition (54).

MiR-29 can target various genes associated with fibrous proteins, including elastin, collagen, and fibrillin. Downregulation of *miR-29* promotes the expression of these fibrous proteins and atrial fibrosis. Decreased *miR-29b* expression was observed in an AF animal model, and after knocking down of *miR-29b in vivo*, the expression of collagen increased (14).

MiR-26 also promotes structural remodeling by regulating the ECM. Harada *et al.* found that in canine and rat models of AF, *miR-26a* was downregulated and transient receptor potential channel 3 (TRPC3) protein was upregulated. The upregulation of TRPC3 was positively correlated with ERK phosphorylation and promoted the expression of ECM-related genes, which could stimulate the proliferation, differentiation, and activation of fibroblasts (33).

MiR-30 and *miR-133* could directly target connective tissue growth factor, and recovery of the normal levels of these miRNAs in myocardial cells may control structural remodeling (55). *MiR-208* is required for cardiomyocyte hypertrophy and fibrosis, and can promote atrial remodeling by inhibiting gap junction protein 40 (56,57). In addition, *miR-499* is significantly upregulated in patients with AF, which could suppress the expression of *CACNB2* and contribute to electrical remodeling (58).

ANR of AF

ANR refers to changes in the density, morphology, and spatial distribution of autonomic nerve fibers after myocardial ischemia, injury, and necrosis. ANR is characterized by nerve regeneration and disordered distribution of nerve fibers that cooperate and promote each other with electrical and structural remodeling, forming a vicious circle, which plays an important role in the pathological process of AF (59).

A study using high-throughput sequencing found that the expression levels of *miR-206* were significantly increased in AF animal models, while superoxide dismutase 1 (*SOD1*) was reported to be the target gene of *miR-206*. Furthermore, studies have also found that *miR-206* can mediate the oxidative stress response via the *SOD1-ROS* and *GCH1-BH4-NO* pathways, and promote ANR as well as the occurrence of AF (14,60). However, besides *miR-206*, no other miRNAs have been directly associated with ANR.

With the continuous in-depth study of miRNAs and the deep understanding of the functions of new miRNAs, significant progress has been made in the fields of miRNAs and AF. The molecular biological mechanism of the occurrence and development of AF has been improved, which relates to the diagnosis and treatment of AF, while prevention provides new strategies. However, most of the current literature lacks comprehensive research, and there remain several gaps in the understanding of the gene regulation of miRNA in AF. In-depth investigation of the expression level and specific mechanism of miRNA in patients with AF as well as targeted regulation of miRNA to prevent and reverse AF will improve AF atrial remodeling and provide new insights into the diagnosis and treatment of AF. *Table 1* summarizes the known miRNAs that participate in atrial remodeling and AF development.

LncRNAs in AF

LncRNAs play an important role in cardiovascular diseases, including AF. Several lncRNAs are not conserved between humans and mice; however, the underlying mechanism of their role in the pathological process of AF remains unclear (64).

Changes in the transcription level of lncRNAs in AF patients

Using microarray and high-throughput sequencing technology to compare the expression of lncRNAs in

Table 1 miRNAs related to AF-associated remodeling

miRNA	Target gene	Remodeling type	References
miRNA-26	KCNJ2	Electrical remodeling	(28)
miRNA-1	KCNE1, KCNB2, KCNJ2		(35)
miRNA-499	KCNN3		(61)
miRNA-328	CACNA1C, CACNB1		(29)
miRNA-208a/b	Unknown		(57)
miRNA-21	SPRY1, TGF-β1	Structure remodeling	(49,62)
miRNA-133	TGF-β1, TGF-βR, CTGF		(53)
miRNA-590	TGF-β1, TGF-βR		(53)
miRNA-208	GJP40		(33)
miRNA-206	SOD1	Autonomic nerve remodeling	(63)

the cardiac tissue of patients with AF and sinus rhythm, numerous studies have found differentially expressed lncRNAs in the cardiac tissue of patients with AF (65-68). Microarray analysis has shown that, compared with patients with sinus rhythm, there were 182 and 219 differentially expressed lncRNAs in the left atrial tissue samples of AF patients, respectively. Another study analyzed the co-expression profile of lncRNAs and mRNAs, and found 177 differentially expressed lncRNAs in AF patients, of which *GATA1*, *EBF1*, and *TAF7* were thought to be involved in the regulation of AF (66). Another study showed that *GATA1* and *TAF1* play an important role in the occurrence and development of AF (69,70). Ke *et al.* also analyzed the differential expression of lncRNAs in the left and right atria of patients with AF and found that two AF-related lncRNAs (*RP3-523K23.2*, *RP11-99E15.2*) regulated heat shock factor 2 (*HSF2*), which is associated with hypertensive heart failure (71). In addition, Chen *et al.* tested the expression profile of lncRNAs in the left atrial appendages and left heart tissues around the pulmonary veins and found 94 differentially expressed lncRNAs. Among them, the most significant changes occurred in *AK055347*, and knock outing could suppress the expression of mitochondrial genes *Cyp450*, ATP synthase, and *MASS51*, which were associated with the decreased viability of H9C2 cardiomyocytes (72). These findings suggest that *AK055347* may act as a regulator of AF by affecting mitochondrial energy production. In summary, by establishing the relationship between the expression of lncRNA and the expression of AF-related gene networks, lncRNAs have been confirmed to be involved in AF. Therefore, we will now focus on lncRNAs related to structure and electrical remodeling in AF.

AF remodeling-related lncRNAs and pathogenic mechanism

LncRNAs are also involved in the remodeling mechanism of AF, and are mainly involved in structural and electrical remodeling. Through pathway enrichment analysis, differentially expressed lncRNAs may induce AF by increasing electrical remodeling and changing the renin-angiotensin system (RAS). However, the mechanisms involved in electrical remodeling are not as clear as those in structural remodeling, which is a chronic pathological process mainly reflected in atrial fibrosis at the level of pathological tissue.

Inflammation putatively plays an important role in the process of fibrosis; in particular, macrophages are known to be involved in atrial fibrosis. The classical classification of macrophages divides them into M1- and M2-type macrophages. M1 macrophages phagocytose cell debris, while M2 macrophages promote tissue repair and healing. Studies have shown that the conversion of M1 to M2 macrophages can prevent cardiac remodeling and improve cardiac function (73). Non-coding repressor of NFAT (*NRON*) is a lncRNA that can bind to the interleukin 12 (*IL-12*) promoter to alleviate atrial fibrosis. M2 type macrophages are stimulated by *IL-12* to induce their conversion to M1 type macrophages, thus leading to atrial fibrosis, which can play a role in inhibiting the nuclear

localization of NFAT. This in turn inhibits the expression of *IL-12* and *IL-12*, which cannot reverse the polarization of macrophages, thereby reducing atrial fibrosis (73). Yu *et al*. compared lncRNAs related to immune signals in lymphocytes from AF and normal sinus rhythm patients and found that there are signaling pathways, such as toll-like receptors (*TLR*) and tumor necrosis factor (*TNF*), between upregulated mRNA and lncRNA co-expression network (74). Through bioinformatics analysis, the authors concluded that lncRNAs from lymphocytes are related to oxidative stress, collagen synthesis, apoptosis, inflammation, and other cellular processes, which are all related to the occurrence of atrial fibrosis.

Studies have shown that lncRNAs can enter the myocardium from the epicardial fat layer by diffusion. The authors collected the epicardial adipose tissue of patients with sinus rhythm and AF patients and found 57 differentially expressed lncRNAs through microarray analysis. These lncRNAs may play a role in inducing atrial fibrosis (75). Meanwhile, Zhao *et al*. (75) found multiple lncRNAs that play a role in atrial fibrosis and are related to protein-coding genes. Of these lncRNAs, the expression of plasmacytoma variant translocation 1 (plasmacytoma variant translocation 1, *PVT1*) is linked to inflammation, lipid metabolism, and *TGF-cad1-induced* epithelial-mesenchymal transition (EMT)-related genes such as *TTC3*, *PDLIM1*, *NOS3*, and *SP1* (75). *TGF-cad1*, a key factor related to the development of atrial fibrosis and AF, often interacts with lncRNAs. Overexpression of *PVT1* can lead to increased fibrosis, while inhibition of *PVT1* can reverse fibrosis. The main molecular mechanism involves *PVT1* acting as a sponge of *miR-128-3p* to regulate the *miR-128-3p/Sp1/TGF-cads1/Smad* axis, which activates the Sp1-mediated *TGF-cads1/Smad* pathway and increases the production of collagen I and II. TGFβ type I receptor kinase (*ALK5*), the downstream target of *TGF-cad1*, regulates cell proliferation (76), including cardiac fibroblasts. Growth inhibitory specificity (*GAS5*) is a lncRNA in cardiomyocytes that can inhibit *ALK5* expression (77). *GAS5* expression is reduced in AF atrial tissues *in vivo*. Inhibition of *GAS5* expression *in vitro* promotes cell growth, while its overexpression inhibits cell growth. In addition to its role in myocardial hypertrophy and fibrosis, myocardial infarction association transcript (*MIAT*) has recently been shown to participate in AF by inhibiting *miR-133-3p* (78). In a rat AF model, the expression of *MIAT* increased in the atrial tissue, whereas the expression of *miR-133-3p* decreased. Knockdown of *MIAT* can inhibit cardiomyocyte apoptosis, indirectly enhance atrial function, and shorten the onset time of AF, thereby reducing AF (79). Another mechanism through which *MIAT* knockdown can alleviate AF is to inhibit AF-induced atrial fibrosis. In addition to *PVT1*, another lncRNA found in AF structural remodeling and fibrosis is long non-coding RNA predicting cardiac remodeling (*lnc LICPAR*) (80). In the atrial muscle tissues of patients, *LICPAR* and *TGF-β1* were upregulated and positively correlated, where *LIPCAR* regulates atrial fibrosis via modulating *TGF-β/Smad* pathway (81).

LncRNAs are also related to the electrical remodeling of AF, but this causal relationship is not as clear as its involvement in structural remodeling. The main driving factors of atrial electrical remodeling are the shortening of the AERP and APD. One gene found in AF is *PITX2*, which is also involved in heart development. Studies have also found that *PITX2* levels in mice prone to AF are relatively low. *PITX2* can affect heart ion channels and change the AERP (82). In addition, we discovered an upstream lncRNA *PITX2* adjacent noncoding RNA (*PANCR*) targeting *PITX2* (83). *PANCR* is not directly related to the development of AF; however, due to the role of *PITX2* in AF, *PANCR* may be an AF-related lncRNA (74). A previous study has tested lncRNAs in rabbits with and without AF, and found that silencing lncRNA *TCONS_00075467* can cause AERP and shorten the APD (84). This may be due to its role as a sponge of *miR-328*, which impedes its inhibitory effect on target mRNA. Due to the loss of this lncRNA, the expression of *miR-328* increases, resulting in the downregulation of the type 1 calcium channel, *CACNA1C*. In fact, dysregulation of *CACNA1C* has been shown to participate in the development of AF by regulating the RAS (29,85). RAS activation is implicated in hypertension and heart failure through AngII, which increases left arterial pressure. In addition, prolonged RAS activation can result in high levels of angiotensin-converting enzyme (ACE) and AngII receptors, leading to an immune response and eventually, fibrosis or structural remodeling (86). In vascular-induced AF mice, upregulated lncRNA and *KCNQ1* overlapping transcript 1 (*KCNQ1OT1*) have been observed. *KCNQ1OT1* can target and silence *CACNA1C* through its sponge function acting on *miR-384*. Excessive *KCNQ1OT1* inhibits the silencing effect of *miR-384*, leading to increased levels of *CACNA1C* and the occurrence of AF (87). A previous study analyzing RNA-seq data from the left and right atrial appendages of patients with AF and sinus rhythm identified key lncRNAs associated with AF (71). The authors suggested that lncRNAs could

Table 2 LncRNAs related to AF-associated remodeling

LncRNA	Target gene	Remodeling type	Reference
PANCR	PITX2	Electrical remodeling	(83)
TCONS_00075467	CACNA1C		(84)
KCNQ1OT1	CACNA1C		(87)
NPPA-AS1	Modulating cardiac contraction genes		(71)
lncRNA-HBL1	miR-1		(89)
PVT1	miR-128-3p/Sp1/TGF-β1/Smad	Structural remodeling	(75)
GAS5	ALK5		(77)
LICPAR	TGF-β1/Smad		(81)
MIAT	miR-133-3p		(78)
NRON	IL-12		(73)
TCONS_00032546	Related to RAS-mediated neuronal remodeling	Nerve remodeling	(88)
TCONS_00026102	Related to RAS-mediated neuronal remodeling		(88)

potentially regulate adjacent genes encoding proteins, and found that lncRNA *NPPA-AS1*, *rp11-99 e15.2*, and *rp3-523 k23.2* may be related to *NPPA*, *ITGB3*, *HSF2*, and in particular *NPPA-AS1*, which was found to interact with *NPPA*. The co-expression of six contractile genes, including *PLCE1*, *TNNC1*, *TACR1*, *GSTO1*, and *TNN1*, suggests that *NPPA-AS1* participates in the pathogenesis of AF by regulating cardiac contraction.

In addition to structural remodeling and electrocardiographic remodeling, nerve remodeling may also be a pathological mechanism of lncRNA-mediated AF. Interestingly, RAS is associated with the autonomic nervous system and participates in nerve remodeling. A previous study has analyzed the lncRNAs in the heart fat pad of dogs with and without AF and found that the abnormally expressed lncRNAs are related to the development, differentiation, and degeneration of neurons (88). The identification of lncRNAs indicates that the inhibition of two lncRNAs related to neural remodeling (*TCONS_00032546* and *TCONS_00026102*) *in vivo* as well as shortening or prolonging the atrial refractory period leads to an increase in the occurrence and prevention of AF. Moreover, the expression of these lncRNAs was negatively correlated with *FGF19*, *FGF4*, *CCND1*, *FGF3*, and *SLC25A4* expression, and these lncRNA genes are adjacent. In summary, these studies indicate that lncRNAs may be involved in the occurrence of AF through RAS-mediated neural remodeling. *Table 2* summarizes the known lncRNAs that participate in atrial remodeling and AF development.

Transcription factors (TFs) and ncRNA

A growing number of evidence suggests that putative gene regulatory networks (GRNs), including cardiac-enriched transcription factors (TFs) and its target genes, can play a potentially important role in the process of adaptive and maladaptive atrial rhythm remodeling (90-92). In addition, the human genome-wide association studies (GWAS) have successfully identified more than 100 genetic sites associated with atrial fibrillation, including genes encoding cardio-enriched TFs (93,94). Most of the GWAS variants associated with AF are located in the non-coding genome (95).

Recently, several studies have documented that cardiac GRNs are controlled by an interlaced network of regulatory ncRNAs, including miRNAs and lncRNAs. The mature miR transcript (approximately 22 nucleotides long) acts as an inhibitor of target gene expression by promoting mRNA degradation or inhibiting translation. In this case, lncRNA (more than 200 nucleotides in length) can activate or inhibit gene expression by adjusting chromatin conformation and TF binding or by isolating miRNA from its target mRNA. Previous research has indicated that ncRNAs are dysregulated in many forms of adult heart disease in patients and animal models (96,97). In particular, a growing body of evidence suggests that ncRNAs may form an additional key layer of complex regulator structure for controlling atrial

Table 3 ncRNAs and TFs in AF

TFs	Cardiac phenotype	Related ncRNAs	Reference
PITX2	Regulates left-right differentiation, lack of which leads to structural and electrical remodeling	miR-17-92, miR-106b-25, miR-21, miR-1, miR-29a, PANCR	(83,85,101-103)
TBX5	Essential for the development of the interventricular septal and atv-ventricular conduction system and the maintenance of the atrial ventricular bundle. TBX5 point mutations are known to cause AF	miR-19, miR-10a/b, RACER	(104-106)
ZFHX3	As a transcriptional inhibitor of myogenic differentiation highly expressed in adult mouse hearts and human stem cell-derived cardiomyoblasts	miR-1	(107)
SHOX2	Controls the development and function of sinoatrial node located in the adult right atrium	miR-92b-5p	(108)

gene expression (84,95,98,99). The perturbation of the expression balance between TF and ncRNA networks can promote the development of AF (100). Therefore, before considering translational therapy strategies, it is necessary to understand the future research of pathways regulated by the atrial TF-miRNA circuit in various AF environments.

Table 3 summarizes the interplay between known cardiac transcription factors and non-coding RNAs in AF.

CircRNAs in AF

CircRNAs are ncRNAs that form a closed-loop structure. Like other ncRNAs, circRNAs play an important role in gene regulation. CircRNAs have been implicated to be closely associated with AF (109). Hu *et al.* found 108 differentially expressed circRNAs in the atrial tissue of patients with persistent AF compared to the myocardial tissue of controls without AF. Among these, 51 circRNAs were upregulated in AF, while 57 were downregulated (110). Genome-wide analysis of AF patients and healthy controls found a total of 14,215 circRNAs, of which 28 were differentially expressed (111).

Shangguan *et al.* analyzed circRNA expression in the atrial tissue of canines with rapid atrial pacing, and found that differentially expressed circRNAs interacted with AF-related miRNAs and mRNAs. This provided a basis for further research into the potential mechanistic roles of circRNAs in AF (112). Zhang *et al.* subsequently proposed a circRNA-related competitive endogenous RNA network in non-valvular persistent AF to better understanding its pathogenesis (113).

Among the circRNAs found to interact with miRNAs, *circRNA19591*, *circRNA19596*, and *circRNA16175* interacted with 36, 28, and 18 different miRNAs, respectively. Additionally, the expression of *miR-29b-1-5p* and *miR-29b-2-5p* is associated with the downregulation of 12 circRNAs (110). CircRNAs have been hypothesized to play a critical role in AF via a sponge regulatory mechanism of miRNAs. In the sponge regulatory technique, the tandem repeat (6× or 8×) miRNA-binding domain is cloned into a vector regulated by the CMV promoter, and the miRNA sponge is transcribed into the cytoplasm in the form of an mRNA, which induces miRNA binding with a similar binding domain in the cytoplasm. It performs sponge-like miRNA absorption and competes with RNA-induced silencing complex (RISC) to bind to free miRNA with a specific RNA-binding domain in the cytoplasm, which can simultaneously inhibit miRNA and the RNA-binding domain (114). In addition, Zhang *et al.* found that *hsa-circ-0000075* and *has-circ-0082096* may be involved in the pathogenesis of AF through the *TGF-β* signaling pathway by targeting the *GDF7* and *IFNG* genes, which are upregulated in the pathway (111).

Conclusion and perspectives

NcRNAs, including miRNAs, lncRNAs, and circRNAs, play an important role in the development of AF. Recent studies have laid a foundation for understanding the molecular mechanisms of AF, and identified ncRNAs that could serve as targets for diagnosis and treatment in the future. The use of ncRNA to treat disease is a promising strategy and may offer new treatment options to patients with AF.

Substantial progress has been made thus far in the area of

ncRNAs as they relate to AF. Multiple ncRNAs have been implicated in the pathological processes underlying AF, including electrical remodeling, structural remodeling, and ANR. Furthermore, with the development of microarray and sequencing technology, the popularity of weighted gene co-expression network analysis (WGCNA) and lncRNA-mRNA co- expression (ceRNA) network analysis, we can identify key modules and hub genes associated with atrial fibrillation more deeply (115,116). We can associate ncRNA with clinical features, which is predicted that there may be small molecule drugs with similar lncRNA or targeted lncRNA therapeutic function in the treatment of AF. When these ncRNAs were employed in the treatment of AF patients, few have achieved a clinical transformation. Many aspects of this research area remain in a preliminary, exploratory stage, such as the emerging roles of circRNAs in AF. However, most of the research has focused only on the relevance of RNA. Moreover, the available data in this area are conflicting, likely due to the complexity of RNA and its transcriptional control, as well as a lack of mechanistic by how RNA acts directly. And because the etiology of AF is very different between human and animal models, it is necessary to use human cells or tissues to develop appropriate disease models (117). Although the AF disease model constructed by human pluripotent stem cells (hPSCs) is becoming one of the basic model of AF and provides a more reliable platform for the study of ncRNA function in AF, there are still many challenges in establishing a mature and stable model to develop new therapies for atrial fibrillation and other cardiovascular diseases and research on ncRNA translation function (118). Thus, further comprehensive research is warranted to address the discrepancies in the literature and the knowledge gaps in this field.

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Footnote

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References

1. Poller W, Dimmeler S, Heymans S, et al. Non-coding RNAs in cardiovascular diseases: diagnostic and therapeutic perspectives. Eur Heart J 2018;39:2704-16.
2. Lip GY, Fauchier L, Freedman SB, et al. Atrial fibrillation. Nat Rev Dis Primers 2016;2:16016.
3. Seccia TM, Caroccia B, Maiolino G, et al. Arterial Hypertension, Aldosterone, and Atrial Fibrillation. Curr Hypertens Rep 2019;21:94.
4. Ferrari R, Bertini M, Blomstrom-Lundqvist C, et al. An update on atrial fibrillation in 2014: From pathophysiology to treatment. Int J Cardiol 2016;203:22-9.
5. Wit AL, Boyden PA. Triggered activity and atrial fibrillation. Heart Rhythm 2007;4:S17-23.
6. Nakao K, Seto S, Ueyama C, et al. Extended distribution of prolonged and fractionated right atrial electrograms predicts development of chronic atrial fibrillation in patients with idiopathic paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2002;13:996-1002.
7. Jones DG, Markides V, Chow AWC, et al. Characterization and consistency of interactions of triggers and substrate at the onset of paroxysmal atrial fibrillation. Europace 2017;19:1454-62.
8. Clauss S, Sinner MF, Kääb S, et al. The Role of MicroRNAs in Antiarrhythmic Therapy for Atrial Fibrillation. Arrhythm Electrophysiol Rev 2015 12;4(3):146-55.
9. S. Babapoor-Farrokhran, D. Gill, R. Rasekhi. The role of

long noncoding RNAs in atrial fibrillation. Heart rhythm 2020;17:1043-9.
10. Liu T, Zhong S, Rao F, et al. Catheter ablation restores decreased plasma miR-409-3p and miR-432 in atrial fibrillation patients. Europace 2016;18:92-9.
11. Liu Z, Zhou C, Liu Y, et al. The expression levels of plasma micoRNAs in atrial fibrillation patients. PLoS One 2012;7:e44906.
12. McManus DD, Tanriverdi K, Lin H, et al. Plasma microRNAs are associated with atrial fibrillation and change after catheter ablation (the miRhythm study). Heart Rhythm 2015;12:3-10.
13. Lu Y, Hou S, Huang D, et al. Expression profile analysis of circulating microRNAs and their effects on ion channels in Chinese atrial fibrillation patients. Int J Clin Exp Med 2015;8:845-53.
14. Dawson K, Wakili R, Ordög B, et al. MicroRNA29: a mechanistic contributor and potential biomarker in atrial fibrillation. Circulation 2013;127:1466-75, 1475e1-28.
15. da Silva AMG, de Araújo JNG, de Oliveira KM, et al. Circulating miRNAs in acute new-onset atrial fibrillation and their target mRNA network. J Cardiovasc Electrophysiol 2018;29:1159-66.
16. McManus DD, Lin H, Tanriverdi K, et al. Relations between circulating microRNAs and atrial fibrillation: data from the Framingham Offspring Study. Heart Rhythm 2014;11:663-9.
17. Böhm A, Vachalcova M, Snopek P, et al. Molecular Mechanisms, Diagnostic Aspects and Therapeutic Opportunities of Micro Ribonucleic Acids in Atrial Fibrillation. Int J Mol Sci 2020;21:2742.
18. Zhelankin AV, Vasiliev SV, Stonogina DA, et al. Elevated Plasma Levels of Circulating Extracellular miR-320a-3p in Patients with Paroxysmal Atrial Fibrillation. Int J Mol Sci 2020;21:3485.
19. Tsoporis JN, Fazio A, Rizos IK, et al. Increased right atrial appendage apoptosis is associated with differential regulation of candidate MicroRNAs 1 and 133A in patients who developed atrial fibrillation after cardiac surgery. J Mol Cell Cardiol 2018;121:25-32.
20. Xiao J, Liang D, Zhang Y, et al. MicroRNA expression signature in atrial fibrillation with mitral stenosis. Physiol Genomics 2011;43:655-64.
21. Nishi H, Sakaguchi T, Miyagawa S, et al. Impact of microRNA expression in human atrial tissue in patients with atrial fibrillation undergoing cardiac surgery. PLoS One 2013;8:e73397.
22. Liu H, Chen GX, Liang MY, et al. Atrial fibrillation alters the microRNA expression profiles of the left atria of patients with mitral stenosis. BMC Cardiovasc Disord 2014;14:10.
23. Cooley N, Cowley MJ, Lin RC, et al. Influence of atrial fibrillation on microRNA expression profiles in left and right atria from patients with valvular heart disease. Physiol Genomics 2012;44:211-9.
24. Yan Y, Shi R, Yu X, et al. Identification of atrial fibrillation-associated microRNAs in left and right atria of rheumatic mitral valve disease patients. Genes Genet Syst 2019;94:23-34.
25. Slagsvold KH, Johnsen AB, Rognmo O, et al. Mitochondrial respiration and microRNA expression in right and left atrium of patients with atrial fibrillation. Physiol Genomics 2014;46:505-11.
26. Slagsvold KH, Johnsen AB, Rognmo O, et al. Comparison of left versus right atrial myocardium in patients with sinus rhythm or atrial fibrillation - an assessment of mitochondrial function and microRNA expression. Physiol Rep 2014;2:e12124.
27. Liu H, Qin H, Chen GX, et al. Comparative expression profiles of microRNA in left and right atrial appendages from patients with rheumatic mitral valve disease exhibiting sinus rhythm or atrial fibrillation. J Transl Med 2014;12:90.
28. Luo X, Pan Z, Shan H, et al. MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. J Clin Invest 2013;123:1939-51.
29. Lu Y, Zhang Y, Wang N, et al. MicroRNA-328 contributes to adverse electrical remodeling in atrial fibrillation. Circulation 2010;122:2378-87.
30. Zhao Y, Huang Y, Li W, et al. Post-transcriptional regulation of cardiac sodium channel gene SCN5A expression and function by miR-192-5p. Biochim Biophys Acta 2015;1852:2024-34.
31. Parkash R, Green MS, Kerr CR, et al. The association of left atrial size and occurrence of atrial fibrillation: a prospective cohort study from the Canadian Registry of Atrial Fibrillation. Am Heart J 2004;148:649-54.
32. Burstein B, Qi XY, Yeh YH, et al. Atrial cardiomyocyte tachycardia alters cardiac fibroblast function: a novel consideration in atrial remodeling. Cardiovasc Res 2007;76:442-52.
33. Harada M, Luo X, Qi XY, et al. Transient receptor potential canonical-3 channel-dependent fibroblast regulation in atrial fibrillation. Circulation 2012;126:2051-64.
34. Chen PS, Chen LS, Fishbein MC, et al. Role of

the autonomic nervous system in atrial fibrillation: pathophysiology and therapy. Circ Res 2014;114:1500-15.
35. Jia X, Zheng S, Xie X, et al. MicroRNA-1 accelerates the shortening of atrial effective refractory period by regulating KCNE1 and KCNB2 expression: an atrial tachypacing rabbit model. PLoS One 2013;8:e85639.
36. Girmatsion Z, Biliczki P, Bonauer A, et al. Changes in microRNA-1 expression and IK1 up-regulation in human atrial fibrillation. Heart Rhythm 2009;6:1802-9.
37. Biliczki P, Boon RA, Girmatsion Z, et al. Age-related regulation and region-specific distribution of ion channel subunits promoting atrial fibrillation in human left and right atria. Europace 2019;21:1261-9.
38. Masè M, Grasso M, Avogaro L, et al. Upregulation of miR-133b and miR-328 in Patients With Atrial Dilatation: Implications for Stretch-Induced Atrial Fibrillation. Front Physiol 2019;10:1133.
39. Terentyev D, Belevych AE, Terentyeva R, et al. miR-1 overexpression enhances Ca(2+) release and promotes cardiac arrhythmogenesis by targeting PP2A regulatory subunit B56alpha and causing CaMKII-dependent hyperphosphorylation of RyR2. Circ Res 2009;104:514-21.
40. Shan H, Zhang Y, Cai B, et al. Upregulation of microRNA-1 and microRNA-133 contributes to arsenic-induced cardiac electrical remodeling. Int J Cardiol 2013;167:2798-805.
41. Feng Z, Takahashi R, Nakamura T, et al. Expression of microRNA-1, microRNA-133a and Hand2 protein in cultured embryonic rat cardiomyocytes. In Vitro Cell Dev Biol Anim 2014;50:700-6.
42. Qi XY, Huang H, Ordog B, et al. Fibroblast inward-rectifier potassium current upregulation in profibrillatory atrial remodeling. Circ Res 2015;116:836-45.
43. Wei C, Kim IK, Kumar S, et al. NF-κB mediated miR-26a regulation in cardiac fibrosis. J Cell Physiol 2013;228:1433-42.
44. Karnabi E, Qu Y, Mancarella S, et al. Rescue and worsening of congenital heart block-associated electrocardiographic abnormalities in two transgenic mice. J Cardiovasc Electrophysiol 2011;22:922-30.
45. Guo L, Qiu Z, Wei L, et al. The microRNA-328 regulates hypoxic pulmonary hypertension by targeting at insulin growth factor 1 receptor and L-type calcium channel-α1C. Hypertension 2012;59:1006-13.
46. Li C, Li X, Gao X, et al. MicroRNA-328 as a regulator of cardiac hypertrophy. Int J Cardiol 2014;173:268-76.
47. Zou R, Kneller J, Leon LJ, et al. Substrate size as a determinant of fibrillatory activity maintenance in a mathematical model of canine atrium. Am J Physiol Heart Circ Physiol 2005;289:H1002-12.
48. Luo X, Yang B, Nattel S. MicroRNAs and atrial fibrillation: mechanisms and translational potential. Nat Rev Cardiol 2015;12:80-90.
49. Adam O, Löhfelm B, Thum T, et al. Role of miR-21 in the pathogenesis of atrial fibrosis. Basic Res Cardiol 2012;107:278.
50. He X, Zhang K, Gao X, et al. Rapid atrial pacing induces myocardial fibrosis by down-regulating Smad7 via microRNA-21 in rabbit. Heart Vessels 2016;31:1696-708.
51. Cardin S, Guasch E, Luo X, et al. Role for MicroRNA-21 in atrial profibrillatory fibrotic remodeling associated with experimental postinfarction heart failure. Circ Arrhythm Electrophysiol 2012;5:1027-35.
52. Cao W, Shi P, Ge JJ. miR-21 enhances cardiac fibrotic remodeling and fibroblast proliferation via CADM1/STAT3 pathway. BMC Cardiovasc Disord 2017;17:88.
53. Shan H, Zhang Y, Lu Y, et al. Downregulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodelling in canines. Cardiovasc Res 2009;83:465-72.
54. Karakikes I, Chaanine AH, Kang S, et al. Therapeutic cardiac-targeted delivery of miR-1 reverses pressure overload-induced cardiac hypertrophy and attenuates pathological remodeling. J Am Heart Assoc 2013;2:e000078.
55. Duisters RF, Tijsen AJ, Schroen B, et al. miR-133 and miR-30 regulate connective tissue growth factor: implications for a role of microRNAs in myocardial matrix remodeling. Circ Res 2009;104:170-8.
56. van Rooij E, Sutherland LB, Qi X, et al. Control of stress-dependent cardiac growth and gene expression by a microRNA. Science 2007;316:575-9.
57. Li S, Jiang Z, Wen L, et al. MicroRNA-208a-3p contributes to connexin40 remolding in human chronic atrial fibrillation. Exp Ther Med 2017;14:5355-62.
58. Ling TY, Wang XL, Chai Q, et al. Regulation of cardiac CACNB2 by microRNA-499: Potential role in atrial fibrillation. BBA Clin 2017;7:78-84.
59. Rahmutula D, Marcus GM, Wilson EE, et al. Molecular basis of selective atrial fibrosis due to overexpression of transforming growth factor-β1. Cardiovasc Res 2013;99:769-79.
60. Wei J, Zhang Y, Li Z, et al. GCH1 attenuates cardiac autonomic nervous remodeling in canines with atrial-tachypacing via tetrahydrobiopterin pathway regulated by microRNA-206. Pacing Clin Electrophysiol 2018;41:459-71.

61. Ling TY, Wang XL, Chai Q, et al. Regulation of the SK3 channel by microRNA-499--potential role in atrial fibrillation. Heart Rhythm 2013;10:1001-9.
62. Tao H, Zhang M, Yang JJ, et al. MicroRNA-21 via Dysregulation of WW Domain-Containing Protein 1 Regulate Atrial Fibrosis in Atrial Fibrillation. Heart Lung Circ 2018;27:104-13.
63. Zhang Y, Zheng S, Geng Y, et al. MicroRNA profiling of atrial fibrillation in canines: miR-206 modulates intrinsic cardiac autonomic nerve remodeling by regulating SOD1. PLoS One 2015;10:e0122674.
64. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol 2014;63:2335-45.
65. Su Y, Li L, Zhao S, et al. The long noncoding RNA expression profiles of paroxysmal atrial fibrillation identified by microarray analysis. Gene 2018;642:125-34.
66. Xu Y, Huang R, Gu J, et al. Identification of long non-coding RNAs as novel biomarker and potential therapeutic target for atrial fibrillation in old adults. Oncotarget 2016;7:10803-11.
67. Ruan Z, Sun X, Sheng H, et al. Long non-coding RNA expression profile in atrial fibrillation. Int J Clin Exp Pathol 2015;8:8402-10.
68. Mei B, Liu H, Yang S, et al. Long non-coding RNA expression profile in permanent atrial fibrillation patients with rheumatic heart disease. Eur Rev Med Pharmacol Sci 2018;22:6940-7.
69. Wirka RC, Gore S, Van Wagoner DR, et al. A common connexin-40 gene promoter variant affects connexin-40 expression in human atria and is associated with atrial fibrillation. Circ Arrhythm Electrophysiol 2011;4:87-93.
70. Gegonne A, Devaiah BN, Singer DS. TAF7: traffic controller in transcription initiation. Transcription 2013;4:29-33.
71. Ke ZP, Xu YJ, Wang ZS, et al. RNA sequencing profiling reveals key mRNAs and long noncoding RNAs in atrial fibrillation. J Cell Biochem 2019. [Epub ahead of print]. doi: 10.1002/jcb.29504.
72. Chen G, Guo H, Song Y, et al. Long non-coding RNA AK055347 is upregulated in patients with atrial fibrillation and regulates mitochondrial energy production in myocardiocytes. Mol Med Rep 2016;14:5311-7.
73. Sun F, Guo Z, Zhang C, et al. LncRNA NRON alleviates atrial fibrosis through suppression of M1 macrophages activated by atrial myocytes. Biosci Rep 2019;39:BSR20192215.
74. Yu XJ, Zou LH, Jin JH, et al. Long noncoding RNAs and novel inflammatory genes determined by RNA sequencing in human lymphocytes are up-regulated in permanent atrial fibrillation. Am J Transl Res 2017;9:2314-26.
75. Zhao L, Ma Z, Guo Z, et al. Analysis of long non-coding RNA and mRNA profiles in epicardial adipose tissue of patients with atrial fibrillation. Biomed Pharmacother 2020;121:109634.
76. Ling LE, Lee WC. Tgf-beta type I receptor (Alk5) kinase inhibitors in oncology. Curr Pharm Biotechnol 2011;12:2190-202.
77. Lu J, Xu FQ, Guo JJ, et al. Long noncoding RNA GAS5 attenuates cardiac fibroblast proliferation in atrial fibrillation via repressing ALK5. Eur Rev Med Pharmacol Sci 2019;23:7605-10.
78. Yao L, Zhou B, You L, et al. LncRNA MIAT/miR-133a-3p axis regulates atrial fibrillation and atrial fibrillation-induced myocardial fibrosis. Mol Biol Rep 2020;47:2605-17.
79. Chen L, Zhang D, Yu L, et al. Targeting MIAT reduces apoptosis of cardiomyocytes after ischemia/reperfusion injury. Bioengineered 2019;10:121-32.
80. Savalan BF, Roozbeh TR, Deanna G, et al. How transforming growth factor contributes to atrial fibrillation? Life Sciences 2021;266:118823.
81. Wang H, Song T, Zhao Y, et al. Long non-coding RNA LICPAR regulates atrial fibrosis via TGF-β/Smad pathway in atrial fibrillation. Tissue Cell 2020;67:101440.
82. Pérez-Hernández M, Matamoros M, Barana A, et al. Pitx2c increases in atrial myocytes from chronic atrial fibrillation patients enhancing IKs and decreasing ICa,L. Cardiovasc Res 2016;109:431-41.
83. Holmes AP, Kirchhof P. Pitx2 Adjacent Noncoding RNA: A New, Long, Noncoding Kid on the 4q25 Block. Circ Arrhythm Electrophysiol 2016;9:e003808.
84. Li Z, Wang X, Wang W, et al. Altered long non-coding RNA expression profile in rabbit atria with atrial fibrillation: TCONS_00075467 modulates atrial electrical remodeling by sponging miR-328 to regulate CACNA1C. J Mol Cell Cardiol 2017;108:73-85.
85. Zhao Y, Yuan Y, Qiu C. Underexpression of CACNA1C Caused by Overexpression of microRNA-29a Underlies the Pathogenesis of Atrial Fibrillation. Med Sci Monit 2016;22:2175-81.
86. Nair GM, Nery PB, Redpath CJ, et al. The Role Of Renin Angiotensin System In Atrial Fibrillation. J Atr Fibrillation 2014;6:972.
87. Shen C, Kong B, Liu Y, et al. YY1-induced upregulation of lncRNA KCNQ1OT1 regulates angiotensin II-induced atrial fibrillation by modulating miR-384b/CACNA1C

axis. Biochem Biophys Res Commun 2018;505:134-40.
88. Wang W, Wang X, Zhang Y, et al. Transcriptome analysis of canine cardiac fat pads: involvement of two novel long non-coding RNAs in atrial fibrillation neural remodeling. J Cell Biochem 2015;116:809-21.
89. Liu J, Li Y, Lin B, et al. HBL1 Is a Human Long Noncoding RNA that Modulates Cardiomyocyte Development from Pluripotent Stem Cells by Counteracting MIR1. Dev Cell 2017;42:333-348.e5.
90. Mikhailov AT, Torrado M. Interplay between cardiac transcription factors and non-coding RNAs in predisposing to atrial fibrillation. J Mol Med (Berl) 2018;96:601-10.
91. Torrado M, Franco D, Lozano-Velasco E, et al. A microRNA-transcription factor blueprint for early atrial arrhythmogenic remodeling. Biomed Res Int 2015;2015:263151.
92. Franco D, Lozano-Velasco E, Aranega A. Gene regulatory networks in atrial fibrillation. World J Med Gen 2016;6:16.
93. Christophersen IE, Rienstra M, Roselli C, et al. Large-scale analyses of common and rare variants identify 12 new loci associated with atrial fibrillation. Nat Genet 2017;49:946-52.
94. Hsu J, Gore-Panter S, Tchou G, et al. Genetic control of left atrial gene expression yields insights into the genetic susceptibility for atrial fibrillation. Circ Genom Precis Med 2018;11:e002107.
95. Tao H, Shi KH, Yang JJ, et al. Epigenetic mechanisms in atrial fibrillation: new insights and future directions. Trends Cardiovasc Med 2016;26:306-18.
96. Kataoka M, Wang DZ. Non-coding RNAs including miRNAs and lncRNAs in cardiovascular biology and disease. Cells 2014;3:883-98.
97. Thum T, Condorelli G. Long noncoding RNAs and microRNAs in cardiovascular pathophysiology. Circ Res 2015;116:751-62.
98. Beermann J, Piccoli MT, et al. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. Physiol Rev 2016;96:1297-325.
99. Molina CE, Voigt N (2017) Finding Ms or Mr Right: which miRNA to target in AF? J Mol Cell Cardiol 102:22-5.
100. van Ouwerkerk AF, Hall AW, Kadow ZA, et al. Epigenetic and Transcriptional Networks Underlying Atrial Fibrillation. Circ Res 2020;127:34-50.
101. Wang J, Bai Y, Li N, et al. Pitx2-microRNA pathway that delimits sinoatrial node development and inhibits predisposition to atrial fibrillation. Proc Natl Acad Sci USA 2014;111:9181-6.
102. Barana A, Matamoros M, Dolz-Gaiton P, et al. Chronic atrial fibrillation increases microRNA-21 in human atrial myocytes decreasing L-type calcium current. Circ Arrhythm Electrophysiol 2014;7:861-8.
103. Chinchilla A, Daimi H, Lozano-Velasco E, et al. PITX2 insufficiency leads to atrial electrical and structural remodeling linked to arrhythmogenesis. Circ Cardiovasc Genet 2011;4:269-79.
104. Chiang DY, Zhang M, Voigt N, et al. Identification of microRNA-mRNA dysregulations in paroxysmal atrial fibrillation. Int J Cardiol 2015;184C:190-7.
105. Wang F, Yang XY, Zhao JY, et al. miR-10a and miR-10b target the 3'-untranslated region of TBX5 to repress its expression. Pediatr Cardiol 2014;35:1072-9.
106. Yang XH, Nadadur RD, Hilvering CR, et al. Transcription-factor-dependent enhancer transcription defines a gene regulatory network for cardiac rhythm. Elife 2017;6:e31683.
107. Huang Y, Wang C, Yao Y, et al. Molecular basis of gene-gene interaction: cyclic cross-regulation of gene expression and post-GWAS gene-gene interaction involved in atrial fibrillation. PLoS Genet 2015;11:e1005393.
108. Hoffmann S, Clauss S, Berger IM, et al. Coding and non-coding variants in the SHOX2 gene in patients with early-onset atrial fibrillation. Basic Res Cardiol 2016;111:e36.
109. Hu X, Chen L, Wu S, et al. Integrative Analysis Reveals Key Circular RNA in Atrial Fibrillation. Front Genet 2019;10:108.
110. Hu M, Wei X, Li M, et al. Circular RNA expression profiles of persistent atrial fibrillation in patients with rheumatic heart disease. Anatol J Cardiol 2019;21:2-10.
111. Zhang PP, Sun J, Li W. Genome-wide profiling reveals atrial fibrillation-related circular RNAs in atrial appendages. Gene 2020;728:144286.
112. Shangguan W, Liang X, Shi W, et al. Identification and characterization of circular RNAs in rapid atrial pacing dog atrial tissue. Biochem Biophys Res Commun 2018;506:1-6.
113. Zhang Y, Ke X, Liu J, et al. Characterization of circRNA-associated ceRNA networks in patients with nonvalvular persistent atrial fibrillation. Mol Med Rep 2019;19:638-50.
114. Liu J, Liu T, Wang X, et al. Circles reshaping the RNA world: from waste to treasure. Mol Cancer 2017;16:58.
115. Liu Y, Liang X, Wang J, et al. Identification of atrial fibrillation-associated lncRNAs and exploration of their functions based on WGCNA and ceRNA network analyses. Gen Physiol Biophys 2021;40:289-305.

116. Liu Y, Liu N, Bai F, et al. Identifying ceRNA Networks Associated With the Susceptibility and Persistence of Atrial Fibrillation Through Weighted Gene Co-Expression Network Analysis. Front Genet 2021;12:653474.
117. Tucker NR, Clauss S, Ellinor PT. Common variation in atrial fibrillation: Navigating the path from genetic association to mechanism. Cardiovasc Res 2016;109:493-501.
118. Goldfracht I, Protze S, Shiti A, et al. Generating ring-shaped engineered heart tissues from ventricular and atrial human pluripotent stem cell-derived cardiomyocytes. Nat Commun 2020;11:75.

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