Non-coding RNAs and Atrial Fibrillation

19

Diego Franco, Amelia Aranega, and Jorge N. Dominguez

Abstract

Atrial fibrillation is the most frequent type of cardiac arrhythmia in humans, with an estimate incidence of 1–2% in the general population, rising up to 8–10% in the elderly. Cardiovascular risk factors such as diabetes, obesity, hypertension and hyperthyroidism can increase the occurrence of AF. The onset of AF triggers additional AF episodes, leading to structural and electrical remodeling of the diseased heart. Understanding the molecular bases of atrial fibrillation have greatly advance over the last decade demonstrating a pivotal role of distinct ion channels in AF pathophysiology. A new scenario has opened on the understanding of the molecular mechanisms underlying AF, with the discovery of non-coding RNAs and their wide implication in multiple disease states, including cardiac arrhythmogenic pathologies. microRNAs are small non-coding RNAs of 22–24 nucleotides that are capable of regulating gene expression by interacting with the mRNA transcript 3′UTRs and promoting mRNA degradation and/or protein translation blockage. Long non-coding RNAs are a more diverse group of non-coding RNAs, providing transcriptional and post-transcriptional roles and subclassified according to their functional properties. In this chapter we summarized current state-of-the-art knowledge on the functional of microRNAs and long non-coding RNAs as well as their cross-talk regulatory mechanisms in atrial fibrillation.

Keywords

microRNAs · lncRNAs · Atrial fibrillation · Biomakers

1 Background

Atrial fibrillation is the most frequent type of cardiac arrhythmia in humans, with an estimate incidence of 1–2% in the general population [1]. In the elderly, AF can rise up to 8–10%. Cardiovascular risk factors such as diabetes, obesity, hypertension and hyperthyroidism can increase the occurrence of AF [2–4]. Importantly, AF can be also secondary to surgical interventions, inflammatory processes and obstructive sleep apnea [5]. The onset of AF triggers additional AF episodes, leading to electrical and structural remodeling of the diseased heart, a condition quoted as "AF begets AF". Electrical remodeling leads to progressive changes in the

D. Franco (✉) · A. Aranega · J. N. Dominguez
Cardiovascular Development Group, Department of Experimental Biology, University of Jaen, Jaen, Spain
e-mail: dfranco@ujaen.es

J. Xiao (ed.), *Non-coding RNAs in Cardiovascular Diseases*, Advances in Experimental Medicine and Biology 1229, https://doi.org/10.1007/978-981-15-1671-9_19

cardiac electrical properties, coursing with early after depolarizations (EADs), delayed after depolarizations (DADs) and/or changes in the action potential duration (APD) configuration culminating thus in rotor formation [6]. Structural remodeling normally courses with atrial fibrosis, inflammation and/or dilatation [7].

Epidemiological studies have undoubtedly demonstrated that cardiovascular risk factors, such as those previously mentioned, enhance AF occurrence. Importantly there are also unquestionable evidences that AF courses in absence of previous risk factors, i.e. a condition dubbed lone AF [8]. Seminal studied by Brugada et al. [9] demonstrate a familiar genetic component in lone AF. Subsequent screening of candidate genes in familiar AF kindreds identified a large number of point mutations in distinct genes encoding for proteins involved in cardiac electrophysiology. Yet, despite this advancement, genetic identification of causative genes in AF only explains 10–15% of all AF patients [10]. In recent years, genome-wide association analyses (GWAS) lightened the discovery of new genes associated to AF. Pioneer worked by Gubdjartsson et al. [11] firstly identify common risk variants highly associated to the onset of lone AF in distinct ethnic cohorts. More recently additional GWAS studies and meta-GWAS have further identified new candidate genes for AF pathophysiology, with over 70 genes potentially involved [12].

Understanding the molecular bases of atrial fibrillation have greatly advance over the last decade. Beside the involvement of genes encoding of distinct ion channels involved in the configuration of the cardiac action potential, the discovery of potential candidate genes by GWAS, and subsequently the functional analyses have unraveled novel pathways [13]. Among them, the most explored to date is driven by Pitx2, leading to Wnt, microRNAs and ion channel remodeling [14–16]. Importantly, a new scenario has opened on the understanding of the molecular mechanisms underlying AF, with the discovery of non-coding RNAs and their wide implication in multiple disease states, including therein cardiac structural and arrhythmogenic pathologies [17].

Non-coding RNAs can be grossly subclassified into two major groups; small non coding RNAs (shorten that 200 nucleotides in length) and long non coding RNAs (longer that 200 nucleotides in length). Small non-coding RNAs contain distinct subclasses such as piwi-RNAs, snoRNAs, siRNAs, and the most numerous and well-studied group of microRNAs [18, 19]. microRNAs are small non-coding RNAs of 22–24 nucleotide that are capable of regulating gene expression by interacting with the mRNA transcript 3′UTRs are promoting mRNA degradation and/or protein translation blockage [20]. Long non-coding RNAs are equally an heterogenous group of non-coding RNAs that are basically subclassified according to their functional properties yet such a classification is complex and imprecise given our limited understanding of their transcriptional and post-transcriptional function [21]. Furthermore, complex interplays between long non coding RNAs and microRNAs are also operative, opening a completely novel landscape of gene regulation.

2 microRNAs as Biomarkers of AF

Non coding RNAs are becoming acknowledged as novel biomarkers in distinct cardiovascular pathologies, including AF (see for recent reviews [22, 23]). Wang et al. [24] recently demonstrated that two distinct microRNAs are significantly decreased in post-ablation AF patients compared to non-ablated AF patients. Importantly, using an experimental model of AF, in pigs, they further corroborated that AF ablation significantly diminished miR-155 and miR-24 expression. Biochemical and molecular analysis demonstrated that these two microRNAs can influence nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) are altered, supporting the role of NO/eNOS pathway in AF. Feldman et al. [25] recently demonstrated that circulating miR-23 and miR-26 were significantly decreased while Harling et al. identified that plasma circulating miR-483 was significantly increased in post-

operative patients developing AF as compared to those that did not develop AF, suggesting a functional role for these microRNAs in the onset of post-operative AF. More recently Liu et al. reported that AF catheter ablation restores miR-409-3p and miR-432 plasma levels, further supporting a pivotal role for microRNAs in AF pathophysiology. Soeki et al. [26] nicely demonstrated that expression of miR-328 and miR-1 were increased in AF patients as compared to control, displaying enhanced expression in the left atrium and pulmonary vein plasma as compared to systemic plasma expression. These evidence support a plausible role for local miR-328 production in relation to atrial substrate remodeling. Similar findings were also reported by Zhou et al. [27]. Overall these data demonstrate that microRNAs might serve as biomarkers to identify and probably to predict the onset and/or course of AF pathophysiology.

3 SNV in microRNAs Associated to AF

Genomic variations on the promoter sequences driving microRNA expression or within the precursors/seed sequences of microRNAs have been reported to be associated to increase rate of AF occurrence. In particular, three distinct microRNAs have been already described, miR-125a, miR-196a2 and miR-146 [28–30]. A miR-125a polymorphism is associated with recurrence of AF after ablation, an association that mechanistically links miR-125a and IL6/IL6R axis, since IL6R is a direct target of miR-125a [28]. A pre-miR-196a2 SNV is associated to increase occurrence of AF in Chinese population, a condition that is also linked with increased atrial dimensions [29]. A polymorphism in miR-146 is a prognostic biomarker for adverse cardiovascular events in AF patients following anticoagulant administration, probably involving inflammatory mechanisms, since IL6/1L6R axis is reversely correlated [30]. In addition, Hoffman et al. [31] reported coding and non-coding variants in SHOX2 gene in patients with atrial fibrillation. Non-coding variants generated a novel functional binding site for miR-92-5p. Importantly, miR-92-5p expression levels in circulating plasma were increased in those patients carrying the SNV, supporting a causative link between SHOX2 non coding SNVs, miR-92-5p expression and AF. In sum, these evidence suggest that impaired regulation of microRNAs expression can have a profound effect on AF occurrence, yet additional experimental evidence is required to fully support these findings.

4 Functional Roles of microRNAs in AF

Multiple microRNAs have been involved in electrical and structural remodeling directly linked to the course of atrial fibrillation. We provide herein evidences on the functional role of microRNAs in cell-cell coupling, electrical regulation, structural impairment as well as in additional signaling pathways related to AF pathology in the following subheadings.

4.1 Functional Roles of microRNAs in Cell-Cell Coupling

Cell-cell coupling exerted by connexin is critical for the correct electrical propagation. Two distinct microRNAs, miR-208a and miR-206, have been reported to target Cx40 and Cx43, respectively [32, 33]. Cx43 has been validated as target of miR-206 by biochemical luciferase assays. Mice over-expressing miR-206 displayed decreased atrial and ventricular Cx43 expression and thus abnormal PR interval and heart rate, leading thereafter to a shortening the life span of these mice [34]. These data postulate a plausible role for miR-208 in AF, although additional evidences are required. Li et al. [35] reported that miR-208 is increased in right atrial biopsies of AF patients, while Cx40 expression was diminished. Experimental studies demonstrate an indirect modulation of Cx40 (Gja5) by miR-208.

Curiously, Takahashi et al. [36] reported that high-fat diet increases vulnerability to atrial arrhythmia by down-regulation of Cx40 via miR-27b.

4.2 Functional Roles of microRNAs in AF Electrical Remodeling

Within the configuration of the cardiac action potential, including sodium and potassium channels. Zhao et al. [37] demonstrate that miR-192 is up-regulated in AF atrial biopsies, while SCN5A is decreased. Luciferase assays demonstrate a direct interaction and regulation of SCN5A by miR-192, leading to modulation of I_{Na} current, supporting a plausible role of these mechanism underlying AF pathophysiology.

Girmatsion et al. [38] demonstrate a complementary expression between miR-1 and Kir2.1 in left atrial AF patients biopsies, data that are concordant with increased IK1 current in LA AF patients as compared to SR patients, while connexin expression was unaffected. Furthermore, *ex vivo* stimulation also lead to similar results, supporting both a key role of miR-1/Kir2.1 in AF pathophysiology and a determinant role suggesting a primary role of atrial rate in miR-1 down-regulation and I(K1) up-regulation. Additional evidence on the role of atrial taquipacing were obtained by Jia et al. [39] using rabbit as experimental model. These authors demonstrate a clear gene expression remodeling up-regulating miR-1 and down-regulating KCNE1 and KCNB2, leading to decrease atrial effecting refractory period while increasing IK currents. In addition, KCNE1 and KCNB2 were corroborated as direct targets of miR-1. Luo et al. [40] reported impaired miR-26 expression in AF patients. Biochemical assays demonstrated that miR-26 regulates KCNJ12 expression. In vitro and in vivo manipulation of miR-26 demonstrate that if impaired, atrial fibrillation develops.

Importantly, most the microRNAs related to AF to date influence calcium homeostasis, a key event regulating onset of AF, including therein miR-21 and miR-29a modulation of CACNA1C [41–42], miR-499 regulation of CACNB2 [43] and miR-106-miR-25 regulation of RyR2 [47]. Zhao et al. [42] demonstrate that CACNA1C is a direct target of miR-21. Barana et al. [41] demonstrate miR-21 expression is up-regulated in AF vs SR atrial myocytes and that miR-21 directly regulates CACNA1C and CACNB2 provoking Ica current changes similar to those recorded in AF patients. Ling et al. [48] and Ling et al. [46] demonstrate that miR-499 directly targets CACNB2 and SK3 channels while miR-499 is significantly increased while CACNB2 and SK3 are decreased in AF patients atrial biopsies. These data similarly support a role of miR-499 in AF pathophysiology. Cañon et al. [49] reported that miR-208b was increased in human and ovine AF biopsies. Over-expression of miR-208 leads to alteration in CACNA1C and CACNB2 and SERCA both at expression and functional levels, supporting a role for miR-208 in AF.

In addition, regulation of HCN by miR-1/miR-133 [47] also plays a role on AF onset with age. Li et al. [47] demonstrate that miR-1 and miR-133 were decreased in age AF right atrial biopsies while HCN2 and HCN4 were up-regulated, supporting a role for these microRNAs in the onset of age-related AF.

Experimental animal models have also provided additional evidences on the functional roles of microRNAs in AF. Chiang et al. [48] demonstrated that deletion of the microRNA-106b-25 cluster in mice promotes atrial fibrillation by enhancing ryanodine receptor type-2 expression and calcium release. Wang et al. [49] and Chinchilla et al. [14] also demonstrated that Pitx2 deficiency disrupt microRNA expression that are linked to atrial arrhythmogenesis, a signaling pathway that also involves regulation of Wnt and Wnt-driven microRNAs expression [15], which is highly susceptible to alteration of cardiovascular risk factors such as hyperthyroidism, hypertension and redox homeostasis imbalance [16]. In dogs, expression of miR-30 and miR-133 is impaired in chronic atrial fibrillation [50] and down-regulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodeling [51].

4.3 Functional Roles of microRNAs in AF Structural Remodeling

Structural remodeling in AF invariably courses with intramyocardial fibrosis. Multiple pathways have been involved in triggering fibrosis and similarly, several reports highlight the functional roles of microRNAs governing this process. Ang-II driven fibrosis is controlled by miR-27 [52], while miR-30c [53] modulated Tgfb-driven fibrosis.

miR-27 can diminished angiotensin II-induced fibrosis, by modulating collagen I/III, plasminogen activator inhibitor type 1 and alpha smooth muscle actin expression by targeting Alk5, a tgf-beta1 receptor as well as inhibiting Smad2/3 phosphorylation without altering Smad1 activity [52]. Furthermore, In isolated perfused hearts, miR-27b restoration markedly attenuated AngII-induced increase in interatrial conduction time, AF incidence and AF duration.

Xu et al. [53] demonstrate that miR-30c directly regulates Tgfbr2 as well as fibroblast proliferation, differentiation, migration and collagen production of cardiac fibroblasts. Therefore, modulating miR-30c expression can provide beneficial effects reversing AF induced atrial fibrosis.

miR-132 influences CTGF activation [54] and miR-30 regulates Snail [58]. Importantly, the most well-described microRNA favouring fibrosis in AF is miR-21, including herein the regulation of CADM1/STAT2 [59], WWP1 [57] as well as other unidentified pathways [58–59]. In addition to fibrosis, structural remodeling in AF also courses with activation of apoptosis. Two distinct microRNAs have been reported to activate apoptosis in AD, miR-122 [60] and miR-1/miR-133 [61].

Quiao et al. [54] demonstrated that miR-132 expression was decreased and CTGF increased in the human and canine models with AF. The expression of miR-132 and CTGF protein levels were upregulated in Ang II stimulated cardiac fibroblasts of adult rats. Furthermore, when miR-132 was introduced into cardiac fibroblasts, the expression of miR-132 increased significantly whereas the expression of CTGF decreased, supporting miR-132 may target CTGF in regulating fibrosis in Ang II-treated cardiac fibroblasts.

Yuan et al. [55] reported an inverse correlation between miR-30a and Snail1 and periostin expression in AngII-induced fibrosis in cardiac fibroblasts. However, the putative mechanisms behind these findings remains unexplored. Cao et al. [56] demonstrated that miR-21 overexpression promotes cardiac fibrosis via STAT3 signaling pathway by decrease CADM1 expression in cell culture models of cardiac fibrosis, supporting that miR-21 might be an important signaling molecule for cardiac fibrotic remodeling and AF.

Tao et al. [57] demonstrated that TGF-β1, collagen I and collagen III levels are significantly elevated in AF patients, miR-21 expression is increased, while the WWP-1 expression was decreased. miR-21 transfected cardiac fibroblasts decreased WWP-1 expression, while opposite effects were observed after miR-21 inhibitor administration. Therefore these data indicated that miR-21 inhibits cardiac fibroblasts proliferation by inactivating the TGF-β1/Smad2 signaling pathway via up-regulation of WWP-1. Yang et al. [62] demonstrated that miR-23b and miR-27b were up-regulated in AF left atrial samples as well as in angiotensin II treated fibroblasts. Overexpression of these microRNAs enhance collagen expression, a process that is TGFBR3 dependent. These data support a functional role for miR-23b and miR-27b in AF fibrosis.

4.4 Functional Roles of microRNAs in Additional AF Related Pathways

Besides electrical and structural remodeling associated to AF, other signaling pathways have been reported to play a role in AF and several microRNAs have been associated to modulate such signaling pathways. Ankyrin B is regulated by miR-34 [63], PTEN/PI3K, STAT3 and Smad7 by miR-21 [64–66] dystrophin by miR-31 [70] and SIRT1 by miR-199 [68]. Overall, these data suggest an increasing important role of microRNAs modulating AF pathophysiology.

5 Transcriptomic Analyses of microRNAs in AF Conditions

Multiple studies have been performed searching for the transcriptomic fingerprints of atrial fibrillation. Some of these studies were exclusively done using a candidate approach on the expression of a limited number of microRNAs, already demonstrating differential expression in human AF. In this context, Da Silva et al. [69] identified increased plasma expression of miR-133b, miR-328 and miR-499 in patients with acute new onset of AF as compared to controls and well-controlled patients. miR-21 on the contrary was decreased in well-controlled patients as compared to controls and new-onset AF patients.

More recently, microRNA microarray analyses provided additional evidences on the differential expression in distinct tissue involved in AF pathogenesis. For example, Zhang et al. [70] analyzed the microRNA fingerprint of the cardiac autonomic nervous plexus and identified 16 differentially expressed microRNAs in atrial taquipaced dogs as compared to controls. These authors further demonstrating that miR-206 controls SOD1 expression, balancing therefore redox homeostasis in atrial taquipaced dogs. In an experimental model of induced AF, Torrado et al. [71] reported the early microRNA signature of AF.

Importantly, great efforts have been devoted to understand the differential contribution of the left and right atrial chambers in AF pathology. Slagsvold et al. [72–73] microRNA array of selected microRNAs between RA and LA, in AF and SR after coronary bypass surgery or valve replacement. They demonstrate rather similar differences between RA and LA atrial analyses in both AF and SR patients, whereas more differences were observed when comparing RA AF vs RA SR and LA AF vs LA SR. In other words, right and left atrial chambers display mostly similar microRNA expression patterns in AF and SR, respectively while AF distinctly affect both RA and LA. Doñate-Puertas et al. [74] analyzed the differential distribution of 662 microRNAs in the left atrium of AF patients with valvular heart disease by microarrays. These authors reported that 42 microRNAs were differentially expressed in AF as compared to controls. A similar report was performed by Liu et al. [75] in AF patients with mitral stenosis. From 1962 microRNAs, only 22 microRNAs were differentially expressed, using microarrays. Xiao et al. [76] similarly investigated differential microRNA expression in AF patients with mitral stenosis but data were obtained from the right atrium instead of the left atrium. Using microarrays against 773 human microRNAs, these authors identified 28 differentially expressed microRNAs. Importantly, side-to-side comparison of the differentially expressed microRNAs in LA AF vs SR resulted in no shared microRNAs between the three distinct studies. Only four microRNAs (miR-18, miR-25, miR-20 and miR-451) were shared by the studies of Slagsvold et al. [72–73] and Doñate-Puertas et al. [74] (Fig. 19.1a). The overall lack of coincidence can be explained on the one hand by a large variability of the human patients cohorts collected on each study, the tissue samples selected or the distinct microRNA microarray platforms used but also it could be attributed to large biological variability that it is current beyond our understanding. Importantly, efforts should be done to solve the puzzle. Secondly, a minimal common microRNA signature is found when comparing LA and RA AF samples (7% of all differentially expressed microRNA in AF samples) (Fig. 19.1b), merging all three studies together, supporting that distinct post-transcriptional regulatory mechanisms are distinct driving AF expression in the LA as compared to the RA.

In addition, a large number of experiments have been performed using whole genome transcriptomics. Cooley et al. [77], Liu et al. [78] and Yan et al. [79] identified the microRNA signature of left and right atrial chambers in the context of AF with valvular heart disease. The authors reported a wide array of microRNA differential gene expression supporting the notion that both AF and valvular heart disease distinct affect the microRNA pattern of both left and right atrial chambers. Importantly, both left and right atrial chambers are distinctly affected by disease progression and by the development of AF. Liu et al.

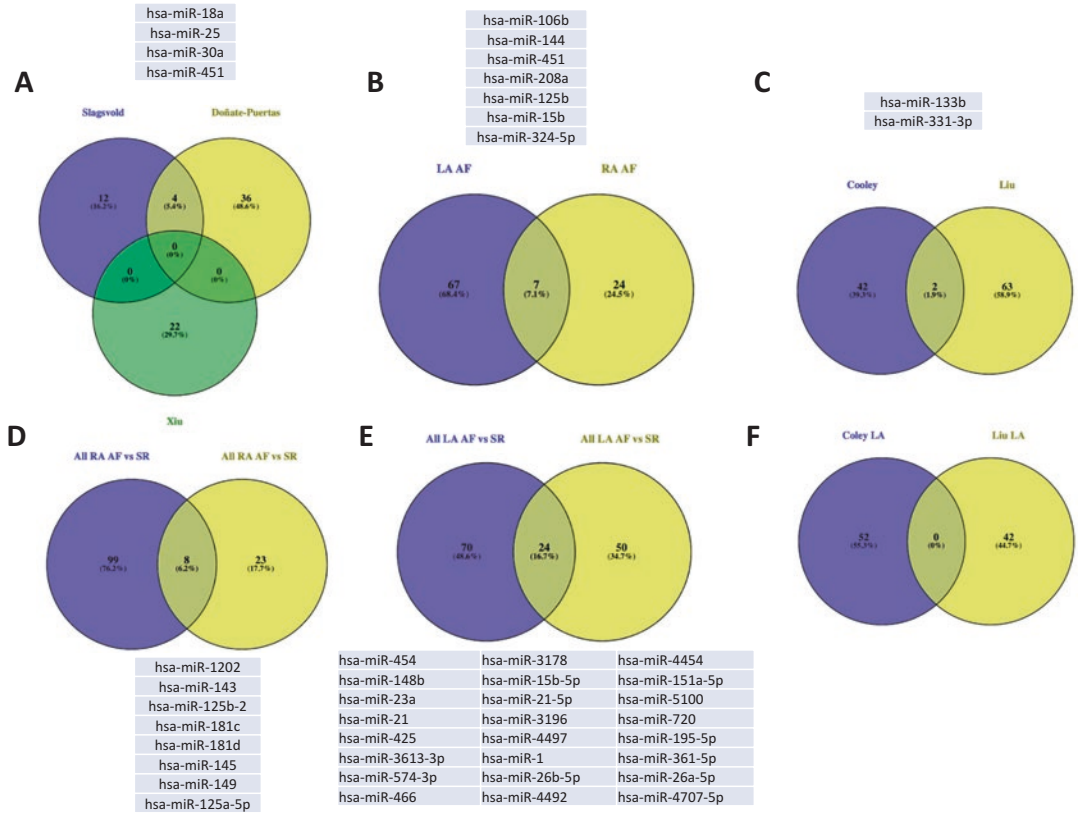

Fig. 19.1 Transcriptomic analyses of microRNAs in AF conditions

[78] reported significant decreased expression of miR-146, miR-150 and miR-199 in blood of patients with paroxysmal and permanent AF, while miR-21 was increased but only in those with permanent AF using massive parallel sequencing.

Surprisingly, a common hallmark of AF is poorly achieved in both RA and LA signatures using massive RNA sequencing technologies; i.e. 2 microRNAs are shared in the RA; miR-133 and miR-331 (Fig. 19.1c); none in LA (Fig. 19.1d). Side-to-side comparison of microarray analyses and RNAseq strategies unraveled a relatively low commonality in the RA AF samples (6.2%; 8 microRNAs) (Fig. 19.1e) but a more robust and significant shared microRNAs in the LA AF (17%; 22 microRNAs) (Fig. 19.1f). Thus, these analyses are promising in providing a core microRNA signature of LA AF remodeling, opening new ways to explore the functional consequences and roles of differentially expressed microRNAs in the context of AF.

However, the large incongruency between studies might be highly related to the large variability on the tissue sample analyzed (systemic plasma, cardiac plasma, atrial biopsies, remnants of cardiac surgery), patients inclusion criteria and methodological approaches used. For example, several studies analyzed differences in AF in the context of valve diseases [74, 76, 78] while only a single study has been reported in absence of valve diseases [80]. In this context Wang et al. [80] analyzed the microRNA expression signature of the LA in AF patients without valve disease by low density microarrays, leading to the identification of 10 differentially expressed microRNAs. Surprisingly, none of the microRNAs in the non valvular AF signature is shared with those previously reported in valvular AF (Fig. 19.2a). Therefore, given the large variability

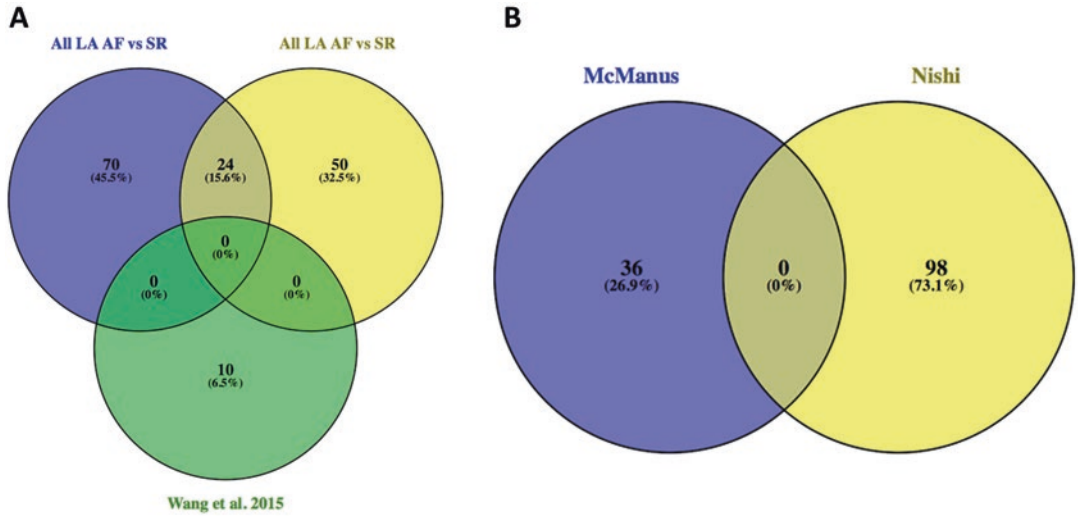

Fig. 19.2 Large variability on the tissue sample analyzed, patients inclusion criteria and methodological approaches used induced large incongruency of microRNAs transcriptomic

of the subjects analyzed, confounding comorbidities such as valvular heart diseases, seems to also greatly influence the microRNA fingerprint of AF, and thus it is hard to find an common AF transcriptomic hallmark.

Transcriptomic analyses were also done in AF post-surgery [81–82]. McManus et al. [84] analyzed 86 microRNAs by qPCR in circulating plasma and atrial tissue samples in patients before and after catheter surgery. They reported 21 differentially expressed microRNAs in AF plasma and 33 up-regulated after surgery. Among these, miR-21 and miR-150 increased threefold, supporting a plausible role for these microRNAs on the regulation of the gene regulatory networks governing AF. Nishi et al. [82] using a similar approach reported 98 differentially expressed microRNA in right atrial samples of AF vs controls. Two microRNAs, miR-21 and miR-208 were elevated after surgery. Interestingly, miRNA-21 expression was highest in patients with chronic AF or an unsuccessful maze procedure, and gradually decreased in order from those with a successful maze procedure to SR patients. Similarly as in previous comparative studies, no microRNA commonality is observed in the results provided by McManus et al. [81] and Nishi et al. [82] (Fig. 19.2b).

6 Emerging Roles of lncRNAs in AF

Our current understanding of the functional roles of long non coding RNAs is on its infancy. Yet solid evidences for the plausible role of discrete lncRNAs in AF have already been provided. For example, Gore-Panter et al. [83] identified PANCR, a lncRNA adjacent to PITX2 in humans. PANCR subcellular localization is mainly cytoplasmic and its expression is independent in sinus rhythm disturbances. Importantly, PANCR silencing significantly modifies PITX2 expression, mimicking thereafter the effects of PITX2 knockdown. However, its current role in AF remains elusive. Shen et al. [84] using a candidate approach analyses reported that KCNQ1OT1 is up-regulated in an AF mouse model as well as in AngII-treated mice. Furthermore these authors demonstrate the functional role of KCNQ1OT1 modulating several electrophysiological parameters such as the effective refractory period and the interatrial conduction. In addition, silencing KCNQ1OT1 leads to diminish the incidence of AF and AF episodes during AngII-treatment. Mechanistically, KCNQ1OT1 regulates CACNA1C by sponging miR-384, supporting thus a pivotal role of this lncRNA in AF

pathophysiology. Zhao et al. [88] investigated the modulative effects of lncRNA TCONS_00202959 on autonomic neural function and myocardial functions in atrial fibrillation rat model. They show that over-expression of this lncRNA in an experimental rat AF model enhances the atrial effective refractory period and diminishes the AF induction rate. More recently, Cao et al. [86] demonstrate increased expression of lncRNA PVT1 in human AF atrial biopsies as compared to controls and they also demonstrate a role for PVT1 directing atrial fibroblast proliferation and collagen deposition by sponging miR-128-3p that in turn facilitated Sp1 expression and thus Tgfb/Smads signaling.

In addition to our knowledge of discrete lncRNA in AF, several studies have been carried out to provide a more global picture of the lncRNA profile in AF. Ruan et al. [87] analyzed by microarray the LA profile of lncRNAs in AF patients with rheumatic valve disease. They identified 219 differentially expressed lncRNAs. Similarly, Mei et al. [88] analyzed the RA profile of lncRNAs in AF patients and identified 182 differentially expressed lncRNA. Wu et al., [89] lncRNA transcriptomic analyses by microarrays using atrial tissue samples (both right and left). 16 lncRNA and 5 mRNA were found to be differentially expressed in AF patients. Chen et al. [90] performed a microarray analyses using pulmonary vein myocardium and the surrounding myocardium and compared to LA appendage. The authors reported 94 differentially expressed lncRNAs, among which AK055347 was one of lncRNAs most significantly altered. Experimental manipulation of this lncRNAs demonstrate a role in mitochondria energy production. Comparison of all the data provides by these authors demonstrate no single match between them (data not shown), raising up the poor robustness of these findings that might be due to technical or biological variables. In addition, how these lncRNAs can influence AF phenotype remains mostly unsolved.

In addition to the lncRNAs hallmark in the AF diseased myocardium, additional studies have been carried out in leucocytes. Su et al. [91] reported the differentially expressed lncRNAs profiles in leucocytes of paroxysmal AF as compared to controls. A total of 2095 lncRNAs were differentially expressed. Two of these lncRNAs (ENST00000559960 and uc004aef.3) were further validated and identified as biomarkers of AF.

Additional evidences on the differential lncRNA expression profile in AF have been reported in two distinct experimental models. Li et al. [92] analyzed the expression profile of lncRNAs by RNAseq in RA samples of experimental rabbit AF model. These authors identified 1220 differentially expressed lncRNAs. They further explore the functional role of one of these differentially expressed lncRNA, i.e. TCONS_00075467, showing that silencing leads to a decrease in L-type calcium current and thus the action potential duration. They further demonstrate that TCONS_00075467 can sponge the microRNA miR-328 and thus regulate the downstream protein CACNA1C, supporting thus a pivotal role in AF pathophysiology. Wang et al. [93] analyzed the lncRNA profile in fat pads from experimental canine model of AF. These authors reported 576 differentially expressed lncRNA (166 down-regulated and 410 up-regulated). In vivo silencing of two of these differentially expressed lncRNAs, TCONS_00032546 and TCONS_00026102, significantly shorten or prolong the atrial effective refractory period thereby increasing or preventing AF inducibility by promoting or inhibiting the neurogenesis, respectively. The lack of evolutionary lncRNA conservation hampers comparison with data obtained in human tissues and thus provides an additional obstacle to dissect the AF lncRNA transcriptomic hallmark.

7 Perspectives

In this study we provide convincing evidence on the functional role of microRNAs and lncRNAs in atrial fibrillation. A wealth of knowledge is currently available of the role of microRNAs in atrial fibrillation, including therein major contributions impacting on both electrical and structural remodeling. In addition several other microRNA-regulated pathways have been

reported although additional experimental evidences are required to fully understand their contribution to AF. Importantly, large discrepancies are observed when transcriptomic analyses are compared. Therefore, efforts should be made to understand the nature of such discrepancy and to search for a common pathways that will serve us to undoubtfully unravel the transcriptomic hallmarks of AF pathophysiology.

Importantly, novel layers of complexity lay ahead of us requiring to decipher gene-gene interactions [94], microRNA-mRNA interactions [95–96] and microRNA-lncRNAs [100] in AF pathophysiology.

Understanding the functional impact of lncRNAs in AF is also major challenge. At present our understanding of lncRNAs is on its infancy. LncRNAs provide a wide array of cellular functions, impacting on both transcriptional and post-transcriptional regulation. They are evolutionarily poorly conserved and our current picture of the transcriptomics profile in AF reflects more controversy and doubts than certainties. Importantly integrative pathways also involved lncRNAs, including microRNAs [97] and mRNAs [98–99] regulation. In addition, disecting whether these non-coding RNAs exert their function in circulating plasma [100–101] or exosome-contained [102] will be of great important to solve current discrepancies. In the next coming years we will witness increasing evidences of the functional impact of lncRNAs in AF pathology as well as od additional non-coding RNAs, i.e. circRNAs, that just entered this arena [103–104].

References

1. Hakim FA, Shen WK. Atrial fibrillation in the elderly: a review. Fut Cardiol. 2014;10:745–58.
2. Abed HS, Wittert GA. Obesity and atrial fibrillation. Obes Rev. 2013;14:929–38.
3. Vargas-Uricoechea H, Sierra-Torres CH. Thyroid hormones and the heart. Horm Mol Biol Clin Investig. 2014;18:15–26.
4. Goudis CA, Korantzopoulos P, Ntalas IV, Kallergis EM, Liu T, Ketikoglou DG. Diabetes mellitus and atrial fibrillation: pathophysiological mechanisms and potential upstream therapies. Int J Cardiol. 2015;184:617–22.
5. Qaddoura A, Kabali C, Drew D, et al. Obstructive sleep apnea as a predictor of atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis. Can J Cardiol. 2014;30:1516–2522.
6. Akoum N, Marrouche N. Assessment and impact of cardiac fibrosis on atrial fibrillation. Curr Cardiol Rep. 2014;16:518.
7. Berenfeld O, Jalife J. Mechanisms of atrial fibrillation: rotors, ionic determinants, and excitation frequency. Cardiol Clin. 2014;32:495–506
8. Potpara TS, Lip GY. A brief history of ‘lone’ atrial fibrillation: from ‘a peculiar pulse irregularity’ to a modern public health concern. Curr Pharm Des. 2015;21:679–96.
9. Brugada R, Tapscott T, Czernuszewicz GZ, et al. Identification of a genetic locus for familial atrial fibrillation. N Engl J Med. 1997;336:905–11.
10. Lozano-Velasco E, Garcia-Padilla C, Aránega AE, Franco D. Genetics of atrial Fibrilation: in search of novel therapeutic targets. Cardiovasc Hematol Disord Drug Targets. 2019 Feb 6.
11. Gudbjartsson DF, Arnar DO, Helgadottir A, Gretarsdottir S, Holm H, Sigurdsson A, Jonasdottir A, Baker A, Thorleifsson G, Kristjansson K, Palsson A, Blondal T, Sulem P, Backman VM, Hardarson GA, Palsdottir E, Helgason A, Sigurjonsdottir R, Sverrisson JT, Kostulas K, Ng MC, Baum L, So WY, Wong KS, Chan JC, Furie KL, Greenberg SM, Sale M, Kelly P, CA MR, Smith EE, Rosand J, Hillert J, Ma RC, Ellinor PT, Thorgeirsson G, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. Variants conferring risk of atrial fibrillation on chromosome 4q25. Nature. 2007 Jul 19;448(7151):353–7.
12. Roselli C, Chaffin MD, Weng LC, Aeschbacher S, Ahlberg G, Albert CM, Almgren P, Alonso A, Anderson CD, Aragam KG, Arking DE, Barnard J, Bartz TM, Benjamin EJ, Bihlmeyer NA, Bis JC, Bloom HL, Boerwinkle E, Bottinger EB, Brody JA, Calkins H, Campbell A, Cappola TP, Carlquist J, Chasman DI, Chen LY, Chen YI, Choi EK, Choi SH, Christophersen IE, Chung MK, Cole JW, Conen D, Cook J, Crijns HJ, Cutler MJ, Damrauer SM, Daniels BR, Darbar D, Delgado G, Denny JC, Dichgans M, Dörr M, Dudink EA, Dudley SC, Esa N, Esko T, Eskola M, Fatkin D, Felix SB, Ford I, Franco OH, Geelhoed B, Grewal RP, Gudnason V, Guo X, Gupta N, Gustafsson S, Gutmann R, Hamsten A, Harris TB, Hayward C, Heckbert SR, Hernesniemi J, Hocking LJ, Hofman A, ARVR H, Huang J, Huang PL, Huffman J, Ingelsson E, Ipek EG, Ito K, Jimenez-Conde J, Johnson R, Jukema JW, Kääb S, Kähönen M, Kamatani Y, Kane JP, Kastrati A, Kathiresan S, Katschnig-Winter P, Kavousi M, Kessler T, Kietselaer BL, Kirchhof P, Kleber ME, Knight S, Krieger JE, Kubo M, Launer LJ, Laurikka J, Lehtimäki T, Leineweber K, Lemaitre RN, Li M, Lim HE, Lin HJ, Lin H, Lind L, Lindgren CM, Lokki ML, London B, RJF L, Low SK, Lu Y, Lyytikäinen LP, Macfarlane PW, Magnusson PK, Mahajan A,

Malik R, Mansur AJ, Marcus GM, Margolin L, Margulies KB, März W, DD MM, Melander O, Mohanty S, Montgomery JA, Morley MP, Morris AP, Müller-Nurasyid M, Natale A, Nazarian S, Neumann B, Newton-Cheh C, Niemeijer MN, Nikus K, Nilsson P, Noordam R, Oellers H, Olesen MS, Orho-Melander M, Padmanabhan S, Pak HN, Paré G, Pedersen NL, Pera J, Pereira A, Porteous D, Psaty BM, Pulit SL, Pullinger CR, Rader DJ, Refsgaard L, Ribasés M, Ridker PM, Rienstra M, Risch L, Roden DM, Rosand J, Rosenberg MA, Rost N, Rotter JI, Saba S, Sandhu RK, Schnabel RB, Schramm K, Schunkert H, Schurman C, Scott SA, Seppälä I, Shaffer C, Shah S, Shalaby AA, Shim J, Shoemaker MB, Siland JE, Sinisalo J, Sinner MF, Slowik A, Smith AV, Smith BH, Smith JG, Smith JD, Smith NL, Soliman EZ, Sotoodehnia N, Stricker BH, Sun A, Sun H, Svendsen JH, Tanaka T, Tanriverdi K, Taylor KD, Teder-Laving M, Teumer A, Thériault S, Trompet S, Tucker NR, Tveit A, Uitterlinden AG, Van Der Harst P, Van Gelder IC, Van Wagoner DR, Verweij N, Vlachopoulou E, Völker U, Wang B, Weeke PE, Weijs B, Weiss R, Weiss S, Wells QS, Wiggins KL, Wong JA, Woo D, Worrall BB, Yang PS, Yao J, Yoneda ZT, Zeller T, Zeng L, Lubitz SA, Lunetta KL, Ellinor PT. Multi-ethnic genome-wide association study for atrial fibrillation. Nat Genet. 2018 Jun 11;50(9):1225–33.

13. Wang J, Klysik E, Sood S, Johnson RL, Wehrens XH, Martin JF. Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification. Proc Natl Acad Sci U S A. 2010 May 25;107(21):9753–8.
14. Chinchilla A, Daimi H, Lozano-Velasco E, Dominguez JN, Caballero R, Delpón E, Tamargo J, Cinca J, Hove-Madsen L, Aranega AE, Franco D. PITX2 insufficiency leads to atrial electrical and structural remodeling linked to arrhythmogenesis. Circ Cardiovasc Genet. 2011 Jun;4(3):269–79.
15. Lozano-Velasco E, Hernández-Torres F, Daimi H, Serra SA, Herraiz A, Hove-Madsen L, Aránega A, Franco D. Pitx2 impairs calcium handling in a dosedependent manner by modulating Wnt signalling. Cardiovasc Res. 2016 Jan 1;109(1):55–66.
16. Lozano-Velasco E, Wangensteen R, Quesada A, Garcia-Padilla C, Osorio JA, Ruiz-Torres MD, Aranega A, Franco D. Hyperthyroidism, but not hypertension, impairs PITX2 expression leading to Wnt-microRNA-ion channel remodeling. PLoS One. 2017 Dec 1;12(12):e0188473.
17. Dueñas A, Expósito A, Aranega A, Franco D. The role of non-coding RNA in congenital heart diseases. J Cardiovasc Dev Dis. 2019 Apr 1;6(2). pii:E15.
18. Lozano-Velasco E, Garcia-Padilla C, Aránega AE, Franco D. Genetics Of Atrial Fibrilation: In Search Of Novel Therapeutic Targets. Cardiovasc Hematol DisordDrug Targets. 2019 Feb 6.
19. Rynkeviciene R, Simiene J, Strainiene E, Stankevicius V, Usinskiene J, Miseikyte Kaubriene E, Meskinyte I, Cicenas J, Suziedelis K. Non-coding RNAs in glioma. Cancers (Basel). 2018 Dec 22;11(1).. pii):E17.
20. Yamamoto T, Saitoh N. Non-coding RNAs and chromatin domains. Curr Opin Cell Biol. 2019 Jan 22;58:26–33.
21. Expósito-Villén A, E Aránega A, Franco D. Functional Role of Non-Coding RNAs during Epithelial-To-Mesenchymal Transition. Noncoding RNA. 2018 May 28;4(2).. pii:E14.
22. Fico A, Fiorenzano A, Pascale E, Patriarca EJ, Minchiotti G. Long non-coding RNA in stem cell pluripotency and lineage commitment: functions and evolutionary conservation. Cell Mol Life Sci. 2019 Apr;76(8):1459–71.
23. Saeedi Borujeni MJ, Esfandiary E, Baradaran A, Valiani A, Ghanadian M, Codoñer-Franch P, Basirat R, Alonso-Iglesias E, Mirzaei H, Yazdani A. Molecular aspects of pancreatic β-cell dysfunction: oxidative stress, microRNA, and long noncoding RNA. J Cell Physiol. 2019 Jun;234(6):8411–25.
24. Orenes-Piñero E, Quintana-Giner M, Romero-Aniorte AI, Valdés M, Marín F. Novel biomarkers in cardiology: MicroRNAs in atrial fibrillation. Arch Cardiol Mex. 2015 Jul-Sep;85(3):225–9.
25. Tsiachris D, Giannopoulos G, Kossyvakis C, Deftereos S, Tsioufis C, Siasos G, Oikonomou E, Gatzoulis K, Tousoulis D, Stefanadis C. Biomarkers determining prognosis of atrial fibrillation ablation. Curr Med Chem. 2018 Mar 20;
26. Wang M, Sun L, Ding W, Cai S, Zhao Q. Ablation alleviates atrial fibrillation by regulating the signaling pathways of endothelial nitric oxide synthase/nitric oxide via miR-155-5p and miR-24-3p. J Cell Biochem. 2019 Mar;120(3):4451–62.
27. Feldman A, Moreira DAR, Gun C, Wang HL, Hirata MH, de Freitas GJ, Leite GGS, Farsky P. Analysis of circulating miR-1, miR-23a, and miR-26a in atrial fibrillation patients undergoing coronary bypass artery grafting surgery. Ann Hum Genet. 2017 May;81(3):99–105.
28. Harling L, Lambert J, Ashrafian H, Darzi A, Gooderham NJ, Athanasiou T. Elevated serum microRNA 483-5p levels may predict patients at risk of postoperative atrial fibrillation. Eur J Cardiothorac Surg. 2017 Jan;51(1):73–8.
29. Liu T, Zhong S, Rao F, Xue Y, Qi Z, Wu S. Catheter ablation restores decreased plasmamiR-409-3p and miR-432 in atrial fibrillation patients. Europace. 2016 Jan;18(1):92–9.
30. Soeki T, Matsuura T, Bando S, Tobiume T, Uematsu E, Ise T, Kusunose K, Yamaguchi K, Yagi S, Fukuda D, Yamada H, Wakatsuki T, Shimabukuro M, Sata M. Relationship between local production of microRNA-328 and atrial substrate remodeling in atrial fibrillation. J Cardiol. 2016 Dec;68(6):472–7.
31. Zhou Q, Maleck C, von Ungern-Sternberg SNI, Neupane B, Heinzmann D, Marquardt J, Duckheim M, Scheckenbach C, Stimpfle F, Gawaz M, Schreieck J, Seizer P, Gramlich M. Circulating MicroRNA-21

correlates with left atrial Low-voltage areas and is associated with procedure outcome in patients undergoing atrial fibrillation ablation. Circ Arrhythm Electrophysiol. 2018 Jun;11(6):e006242.
32. Shen XB, Zhang SH, Li HY, Chi XD, Jiang L, Huang QL, Xu SH. Rs12976445 Polymorphism is associated with post-ablation recurrence of atrial fibrillation by modulating the expression of MicroRNA-125a and interleukin-6R. Med Sci Monit. 2018 Sep 11;24:6349–58.
33. Su YM, Li J, Guo YF, Cai F, Cai XX, Pan HY, Deng XT, Pan M. A functional single-nucleotide polymorphism in pre-microRNA-196a2 is associated with atrial fibrillation in Han Chinese. Clin Lab. 2015;61(9):1179–85.
34. Jin Y, Zhou TY, Cao JN, Feng QT, Fu YJ, Xu X, Yang CJ. MicroRNA-206 downregulates Connexin43 in cardiomyocytes to induce cardiac arrhythmias in a transgenic mouse model. Heart Lung Circ. 2018 Oct 4;S1443–9506(18). pii:): 31917–6.
35. Li S, Jiang Z, Wen L, Feng G, Zhong G. MicroRNA-208a-3p contributes to connexin40 remolding in human chronic atrial fibrillation. Exp Ther Med. 2017 Dec;14(6):5355–62.
36. Takahashi K, Sasano T, Sugiyama K, Kurokawa J, Tamura N, Soejima Y, Sawabe M, Isobe M, Furukawa T. High-fat diet increases vulnerability to atrial arrhythmia by conduction disturbance via miR-27b. J Mol Cell Cardiol. 2016 Jan;90:38–46.
37. Zhao Y, Huang Y, Li W, Wang Z, Zhan S, Zhou M, Yao Y, Zeng Z, Hou Y, Chen Q, Tu X, Wang QK, Huang Z. Post-transcriptional regulation of cardiac sodium channel gene SCN5A expression and function by miR-192-5p. Biochim Biophys Acta. 2015 Oct;1852(10 Pt A):2024–34.
38. Girmatsion Z, Biliczki P, Bonauer A, Wimmer-Greinecker G, Scherer M, Moritz A, Bukowska A, Goette A, Nattel S, Hohnloser SH, Ehrlich JR. Changes in microRNA-1 expression and IK1 up-regulation in human atrial fibrillation. Heart Rhythm. 2009 Dec;6(12):1802–9.
39. Jia X, Zheng S, Xie X, Zhang Y, Wang W, Wang Z, Zhang Y, Wang J, Gao M, Hou Y. MicroRNA-1 accelerates the shortening of atrial effective refractory period by regulating KCNE1 and KCNB2 expression: an atrial tachypacing rabbit model. PLoS One. 2013 Dec 30;8(12):e85639.
40. Luo X, Pan Z, Shan H, Xiao J, Sun X, Wang N, Lin H, Xiao L, Maguy A, Qi XY, Li Y, Gao X, Dong D, Zhang Y, Bai Y, Ai J, Sun L, Lu H, Luo XY, Wang Z, Lu Y, Yang B, Nattel S. MicroRNA-26 governs profibrillatory inward-rectifier potassium current changes in atrial fibrillation. J Clin Invest. 2013 May;123(5):1939–51.
41. Barana A, Matamoros M, Dolz-Gaitón P, Pérez-Hernández M, Amorós I, Núñez M, Sacristán S, Pedraz Á, Pinto Á, Fernández-Avilés F, Tamargo J, Delpón E, Caballero R. Chronic atrial fibrillation increases microRNA-21 in human atrial myocytes decreasing L-type calcium current. Circ Arrhythm Electrophysiol. 2014 Oct;7(5):861–8.
42. 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 Jun 24;22:2175–81.
43. Ling TY, Wang XL, Chai Q, Lu T, Stulak JM, Joyce LD, Daly RC, Greason KL, Wu LQ, Shen WK, Cha YM, Lee HC. Regulation of cardiac CACNB2 by microRNA-499: potential role in atrial fibrillation. BBA Clin. 2017 Feb 9;7:78–84.
44. Chiang DY, Zhang M, Voigt N, Alsina KM, Jakob H, Martin JF, Dobrev D, Wehrens XH, Li N. Identification of microRNA-mRNA dysregulations in paroxysmal atrial fibrillation. Int J Cardiol. 2015 Apr 1;184:190–7.
45. Ling TY, Wang XL, Chai Q, Lau TW, Koestler CM, Park SJ, Daly RC, Greason KL, Jen J, Wu LQ, Shen WF, Shen WK, Cha YM, Lee HC. Regulation of the SK3 channel by microRNA-499DOUBLE-HYPHENpotential role in atrial fibrillation. Heart Rhythm. 2013 Jul;10(7):1001–9.
46. Cañón S, Caballero R, Herraiz-Martínez A, Pérez-Hernández M, López B, Atienza F, Jalife J, Hove-Madsen L, Delpón E, Bernad A. miR-208b upregulation interferes with calcium handling in HL-1 atrial myocytes: implications in human chronic atrial fibrillation. J Mol Cell Cardiol. 2016 Oct;99:162–73.
47. Li YD, Hong YF, Yusufuaji Y, Tang BP, Zhou XH, Xu GJ, Li JX, Sun L, Zhang JH, Xin Q, Xiong J, Ji YT, Zhang Y. Altered expression of hyperpolarizationactivated cyclic nucleotide-gated channels and microRNA-1 and -133 in patients with age-associated atrial fibrillation. Mol Med Rep. 2015 Sep;12(3):3243–8.
48. Chiang DY, Kongchan N, Beavers DL, Alsina KM, Voigt N, Neilson JR, Jakob H, Martin JF, Dobrev D, Wehrens XH, Li N. Loss of microRNA-106b-25 cluster promotes atrial fibrillation by enhancing ryanodine receptor type-2 expression and calcium release. Circ Arrhythm Electrophysiol. 2014 Dec;7(6):1214–22.
49. Wang J, Bai Y, Li N, Ye W, Zhang M, Greene SB, Tao Y, Chen Y, Wehrens XH, Martin JF. Pitx2-microRNA pathway that delimits sinoatrial node development and inhibits predisposition to atrial fibrillation. Proc Natl Acad Sci U S A. 2014 Jun 24;111(25):9181–6.
50. Li H, Li S, Yu B, Liu S. Expression of miR-133 and miR-30 in chronic atrial fibrillation in canines. Mol Med Rep. 2012 Jun;5(6):1457–60.
51. Shan H, Zhang Y, Lu Y, Zhang Y, Pan Z, Cai B, Wang N, Li X, Feng T, Hong Y, Yang B. Downregulation of miR-133 and miR-590 contributes to nicotine-induced atrial remodelling in canines. Cardiovasc Res. 2009 Aug 1;83(3):465–72.
52. Wang Y, Cai H, Li H, Gao Z, Song K. Atrial overexpression of microRNA-27b attenuates angiotensin II-induced atrial fibrosis and fibrillation by targeting ALK5. Hum Cell. 2018 Jul;31(3):251–60.

53. Xu J, Wu H, Chen S, Qi B, Zhou G, Cai L, Zhao L, Wei Y, Liu S. MicroRNA-30c suppresses the profibrogenic effects of cardiac fibroblasts induced by TGF-β1 and prevents atrial fibrosis by targeting TGFβRII. J Cell Mol Med. 2018 Jun;22(6):3045–57.
54. Qiao G, Xia D, Cheng Z, Zhang G. miR-132 in atrial fibrillation directly targets connective tissue growth factor. Mol Med Rep. 2017 Oct;16(4):4143–50.
55. Yuan CT, Li XX, Cheng QJ, Wang YH, Wang JH, Liu CL. MiR-30a regulates the atrial fibrillation-induced myocardial fibrosis by targeting snail 1. Int J Clin Exp Pathol. 2015 Dec 1;8(12):15527–36.
56. Cao W, Shi P, Ge JJ. miR-21 enhances cardiac fibrotic remodeling and fibroblast proliferation via CADM1/STAT3 pathway. BMC Cardiovasc Disord. 2017 Mar 23;17(1):88.
57. Tao H, Zhang M, Yang JJ, Shi KH. MicroRNA-21 via dysregulation of WW domain-containing protein 1 regulate atrial fibrosis in atrial fibrillation. Heart Lung Circ. 2018 Jan;27(1):104–13.
58. Cardin S, Guasch E, Luo X, Naud P, Le Quang K, Shi Y, Tardif JC, Comtois P, Nattel S. Role for MicroRNA-21 in atrial profibrillatory fibrotic remodeling associated with experimental postinfarction heart failure. Circ Arrhythm Electrophysiol. 2012 Oct;5(5):1027–35.
59. Adam O, Löhfelm B, Thum T, Gupta SK, Puhl SL, Schäfers HJ, Böhm M, Laufs U. Role of miR-21 in the pathogenesis of atrial fibrosis. Basic Res Cardiol. 2012 Sep;107(5):278.
60. Zhang X, Jing W. Upregulation of miR-122 is associated with cardiomyocyte apoptosis in atrial fibrillation. Mol Med Rep. 2018 Aug;18(2):1745–51.
61. Tsoporis JN, Fazio A, Rizos IK, Izhar S, Proteau G, Salpeas V, Rigopoulos A, Sakadakis E, Toumpoulis IK, Parker TG. 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 Aug;121:25–32.
62. Yang Z, Xiao Z, Guo H, Fang X, Liang J, Zhu J, Yang J, Li H, Pan R, Yuan S, Dong W, Zheng XL, Wu S, Shan Z. Novel role of the clustered miR-23b-3p and miR-27b-3p in enhanced expression of fibrosis-associated genes by targeting TGFBR3 in atrial fibroblasts. J Cell Mol Med. 2019 Feb;7
63. Zhu Y, Feng Z, Cheng W, Xiao Y. MicroRNA-34a mediates atrial fibrillation through regulation of Ankyrin-B expression. Mol Med Rep. 2018 Jun;17(6):8457–65.
64. Zhang K, Zhao L, Ma Z, Wang W, Li X, Zhang Y, Yuan M, Liang X, Li G. Doxycycline attenuates atrial remodeling by interfering with MicroRNA-21 and downstream phosphatase and Tensin homolog (PTEN)/phosphoinositide 3-kinase (PI3K) signaling pathway. Med Sci Monit. 2018 Aug 11;24:5580–7.
65. Huang Z, Chen XJ, Qian C, Dong Q, Ding D, Wu QF, Li J, Wang HF, Li WH, Xie Q, Cheng X, Zhao N, Du YM, Liao YH. Signal transducer and activator of transcription 3/MicroRNA-21 feedback loop contributes to atrial fibrillation by promoting atrial fibrosis in a rat sterile pericarditis model. Circ Arrhythm Electrophysiol. 2016 Jul;9(7). pii:e003396.
66. He X, Zhang K, Gao X, Li L, Tan H, Chen J, Zhou Y. Rapid atrial pacing induces myocardial fibrosis by down-regulating Smad7 via microRNA-21 in rabbit. Heart Vessel. 2016 Oct;31(10):1696–708.
67. Reilly SN, Liu X, Carnicer R, Recalde A, Muszkiewicz A, Jayaram R, Carena MC, Wijesurendra R, Stefanini M, Surdo NC, Lomas O, Ratnatunga C, Sayeed R, Krasopoulos G, Rajakumar T, Bueno-Orovio A, Verheule S, Fulga TA, Rodriguez B, Schotten U, Casadei B. Up-regulation of miR-31 in human atrial fibrillation begets the arrhythmia by depleting dystrophin and neuronal nitric oxide synthase. Sci Transl Med. 2016 May 25;8(340):340ra74.
68. Yamac AH, Kucukbuzcu S, Ozansoy M, Gok O, Oz K, Erturk M, Yilmaz E, Ersoy B, Zeybek R, Goktekin O, Kilic U. Altered expression of microRNA 199a and increased levels of cardiac SIRT1 protein are associated with the occurrence of atrial fibrillation after coronary artery bypass graft surgery. Cardiovasc Pathol. 2016 May-Jun;25(3):232–6.
69. da Silva AMG, de Araújo JNG, de Oliveira KM, Novaes AEM, Lopes MB, de Sousa JCV, Filho AAA, Luchessi AD, de Rezende AA, Hirata MH, Silbiger VN. Circulating miRNAs in acute new-onset atrial fibrillation and their target mRNA network. J Cardiovasc Electrophysiol. 2018 Aug;29(8):1159–66.
70. Zhang Y, Zheng S, Geng Y, Xue J, Wang Z, Xie X, Wang J, Zhang S, Hou Y. MicroRNA profiling of atrial fibrillation in canines: miR-206 modulates intrinsic cardiac autonomic nerve remodeling by regulating SOD1. PLoS One. 2015 Mar 27;10(3):e0122674.
71. Torrado M, Franco D, Lozano-Velasco E, Hernández-Torres F, Calviño R, Aldama G, Centeno A, Castro-Beiras A, Mikhailov A. A MicroRNA-transcription factor blueprint for early atrial Arrhythmogenic remodeling. Biomed Res Int. 2015;2015:263151.
72. Slagsvold KH, Johnsen AB, Rognmo O, Høydal M, Wisløff U, Wahba A. 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 Aug 28;2(8). pii:e12124.
73. Slagsvold KH, Johnsen AB, Rognmo O, Høydal MA, Wisløff U, Wahba A. Mitochondrial respiration and microRNA expression in right and left atrium of patients with atrial fibrillation. Physiol Genomics. 2014 Jul 15;46(14):505–11.
74. Doñate Puertas R, Jalabert A, Meugnier E, Euthine V, Chevalier P, Rome S. Analysis of the microRNA signature in left atrium from patients with valvular heart disease reveals their implications in atrial fibrillation. PLoS One. 2018 May 3;13(5):e0196666.
75. Liu H, Chen GX, Liang MY, Qin H, Rong J, Yao JP, Wu ZK. Atrial fibrillation alters the microRNA

expression profiles of the left atria of patients with mitral stenosis. BMC Cardiovasc Disord. 2014 Jan 25;14:10.
76. Xiao J, Liang D, Zhang Y, Liu Y, Zhang H, Liu Y, Li L, Liang X, Sun Y, Chen YH. MicroRNA expression signature in atrial fibrillation with mitral stenosis. Physiol Genomics. 2011 Jun 15;43(11):655–64.
77. Cooley N, Cowley MJ, Lin RC, Marasco S, Wong C, Kaye DM, Dart AM, Woodcock EA. Influence of atrial fibrillation on microRNA expression profiles in left and right atria from patients with valvular heart disease. Physiol Genomics. 2012 Feb 13;44(3):211–9.
78. Liu H, Qin H, Chen GX, Liang MY, Rong J, Yao JP, Wu ZK. 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 Apr 6;12:90.
79. Yan Y, Shi R, Yu X, Sun C, Zang W, Tian H. Identification of atrial fibrillation-associated microRNAs in left and right atria of rheumatic mitral valve disease patients. Genes Genet Syst. 2018 Dec 24;
80. Wang J, Song S, Xie C, Han J, Li Y, Shi J, Xin M, Wang J, Luo T, Meng X, Yang B. MicroRNA profiling in the left atrium in patients with non-valvular paroxysmal atrial fibrillation. BMC Cardiovasc Disord. 2015 Aug 29;15:97.
81. McManus DD, Tanriverdi K, Lin H, Esa N, Kinno M, Mandapati D, Tam S, Okike ON, Ellinor PT, Keaney JF Jr, Donahue JK, Benjamin EJ, Freedman JE. Plasma microRNAs are associated with atrial fibrillation and change after catheter ablation (the miRhythm study). Heart Rhythm. 2015 Jan;12(1):3–10.
82. Nishi H, Sakaguchi T, Miyagawa S, Yoshikawa Y, Fukushima S, Saito S, Ueno T, Kuratani T, Sawa Y. Impact of microRNA expression in human atrial tissue in patients with atrial fibrillation undergoing cardiac surgery. PLoS One. 2013 Sep 12;8(9):e73397.
83. Gore-Panter SR, Hsu J, Barnard J, Moravec CS, Van Wagoner DR, Chung MK, Smith JD. PANCR, the PITX2 adjacent noncoding RNA, is expressed in human left atria and regulates PITX2c expression. Circ Arrhythm Electrophysiol. 2016 Jan;9(1):e003197.
84. Shen C, Kong B, Liu Y, Xiong L, Shuai W, Wang G, Quan D, Huang H. YY1-induced upregulation of lncRNA KCNQ1OT1 regulates angiotensin II-induced atrial fibrillation by modulating miR-384b/CACNA1C axis. Biochem Biophys Res Commun. 2018 Oct 20;505(1):134–40.
85. Zhao JB, Zhu N, Lei YH, Zhang CJ, Li YH. Modulative effects of lncRNA TCONS_00202959 on autonomic neural function and myocardial functions in atrial fibrillation rat model. Eur Rev Med Pharmacol Sci. 2018 Dec;22(24):8891–7.
86. Cao F, Li Z, Ding WM, Yan L, Zhao QY. LncRNA PVT1 regulates atrial fibrosis via miR-128-3p-SP1-TGF-β1-Smad axis in atrial fibrillation. Mol Med. 2019 Mar 20;25(1):7.
87. Ruan Z, Sun X, Sheng H, Zhu L. Long non-coding RNA expression profile in atrial fibrillation. Int J Clin Exp Pathol. 2015 Jul 1;8(7):8402–10.
88. Mei B, Liu H, Yang S, Liang MY, Yue Y, Huang SQ, Hou J, Chen GX, Wu ZK. Long non-coding RNA expression profile in permanent atrial fibrillation patients with rheumatic heart disease. Eur Rev Med Pharmacol Sci. 2018 Oct;22(20):6940–7.
89. Wu J, Han D, Shi R, Chen M, Sun J, Tian H, Yan Y. Identification of atrial fibrillation-associated lncRNAs in atria from patients with rheumatic mitral valve disease. Microsc Res Tech. 2019 Apr 11;
90. Chen G, Guo H, Song Y, Chang H, Wang S, Zhang M, Liu C. Long non-coding RNA AK055347 is upregulated in patients with atrial fibrillation and regulates mitochondrial energy production in myocardiocytes. Mol Med Rep. 2016 Dec;14(6):5311–7.
91. Su Y, Li L, Zhao S, Yue Y, Yang S. The long non-coding RNA expression profiles of paroxysmal atrial fibrillation identified by microarray analysis. Gene. 2018 Feb 5;642:125–34.
92. Li Z, Wang X, Wang W, Du J, Wei J, Zhang Y, Wang J, Hou Y. 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 Jul;108:73–85.
93. Wang W, Wang X, Zhang Y, Li Z, Xie X, Wang J, Gao M, Zhang S, Hou Y. Transcriptome analysis of canine cardiac fat pads: involvement of two novel long non-coding RNAs in atrial fibrillation neural remodeling. J Cell Biochem. 2015 May;116(5):809–21.
94. Huang Y, Wang C, Yao Y, Zuo X, Chen S, Xu C, Zhang H, Lu Q, Chang L, Wang F, Wang P, Zhang R, Hu Z, Song Q, Yang X, Li C, Li S, Zhao Y, Yang Q, Yin D, Wang X, Si W, Li X, Xiong X, Wang D, Huang Y, Luo C, Li J, Wang J, Chen J, Wang L, Wang L, Han M, Ye J, Chen F, Liu J, Liu Y, Wu G, Yang B, Cheng X, Liao Y, Wu Y, Ke T, Chen Q, Tu X, Elston R, Rao S, Yang Y, Xia Y, Wang QK. 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 Aug 12;11(8):e1005393.
95. Wang T, Wang B. Identification of microRNA-mRNA interactions in atrial fibrillation using microarray expression profiles and bioinformatics analysis. Mol Med Rep. 2016 Jun;13(6):4535–40.
96. Wang J, Wang Y, Han J, Li Y, Xie C, Xie L, Shi J, Zhang J, Yang B, Chen D, Meng X. Integrated analysis of microRNA and mRNA expression profiles in the left atrium of patients with nonvalvular paroxysmal atrial fibrillation: role of miR-

146b-5p in atrial fibrosis. Heart Rhythm. 2015 May;12(5):1018–26.
97. Qian C, Li H, Chang D, Wei B, Wang Y. Identification of functional lncRNAs in atrial fibrillation by integrative analysis of the lncRNA-mRNA network based on competing endogenous RNAs hypothesis. J Cell Physiol. 2018 Nov;27
98. Yu XJ, Zou LH, Jin JH, Xiao F, Li L, Liu N, Yang JF, Zou T. 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 May 15;9(5):2314–26.
99. Xu Y, Huang R, Gu J, Jiang W. Identification of long non-coding RNAs as novel biomarker and potential therapeutic target for atrial fibrillation in old adults. Oncotarget. 2016 Mar 8;7(10):10803–11.
100. Lu Y, Hou S, Huang D, Luo X, Zhang J, Chen J, Xu W. Expression profile analysis of circulating microRNAs and their effects on ion channels in Chinese atrial fibrillation patients. Int J Clin Exp Med. 2015 Jan 15;8(1):845–53.
101. Natsume Y, Oaku K, Takahashi K, Nakamura W, Oono A, Hamada S, Yamazoe M, Ihara K, Sasaki T, Goya M, Hirao K, Furukawa T, Sasano T. Combined analysis of human and experimental murine samples identified novel circulating MicroRNAs as biomarkers for atrial fibrillation. Circ J. 2018 Mar 23;82(4):965–73.
102. Mun D, Kim H, Kang JY, Park H, Park H, Lee SH, Yun N, Joung B. Expression of miRNAs in circulating exosomes derived from patients with persistent atrial fibrillation. FASEB J. 2019 Feb 12:fj201801758R.
103. Hu M, Wei X, Li M, Tao L, Wei L, Zhang M, Cheng H, Yuan Y. Circular RNA expression profiles of persistent atrial fibrillation in patients with rheumatic heart disease. Anatol J Cardiol. 2019 Jan;21(1):2–10.
104. Zhang Y, Ke X, Liu J, Ma X, Liu Y, Liang D, Wang L, Guo C, Luo Y. Characterization of circRNA-associated ceRNA networks in patients with nonvalvular persistent atrial fibrillation. Mol Med Rep. 2019 Jan;19(1):638–50.