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Interplay between cardiac transcription factors and non-coding RNAs in predisposing to atrial fibrillation

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Abstract

There is growing evidence that putative gene regulatory networks including cardio-enriched transcription factors, such as *PITX2*, *TBX5*, *ZFHX3*, and *SHOX2*, and their effector/target genes along with downstream non-coding RNAs can play a potentially important role in the process of adaptive and maladaptive atrial rhythm remodeling. In turn, expression of atrial fibrillation-associated transcription factors is under the control of upstream regulatory non-coding RNAs. This review broadly explores gene regulatory mechanisms associated with susceptibility to atrial fibrillation—with key examples from both animal models and patients—within the context of both cardiac transcription factors and non-coding RNAs. These two systems appear to have multiple levels of cross-regulation and act coordinately to achieve effective control of atrial rhythm effector gene expression. Perturbations of a dynamic expression balance between transcription factors and corresponding non-coding RNAs can provoke the development or promote the progression of atrial fibrillation. We also outline deficiencies in current models and discuss ongoing studies to clarify remaining mechanistic questions. An understanding of the function of transcription factors and non-coding RNAs in gene regulatory networks associated with atrial fibrillation risk will enable the development of innovative therapeutic strategies.

Keywords

Atrial fibrillation; Gene regulatory networks; Transcription factors; Non-coding RNAs; Atrial myocardium

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in current clinical practice. There are different predisposing risk factors and conditions for the development of AF, but patients diagnosed with asymptomatic non-familiar AF do not have any traditional risk factors. Proarrhythmogenic molecular remodeling, broadly defined as any change in atrial gene regulation that promotes atrial conduction disturbances, is potentially crucial for unraveling a sudden-onset of AF [1].

There is growing evidence that putative gene regulatory networks (GRNs) including cardio-enriched transcription factors (TFs) and their target genes can play a potentially important role in the process of adaptive and maladaptive atrial rhythm remodeling [2]. In addition, human genome-wide association studies (GWAS) have successfully identified chromosome loci of DNA variants associated with increasing risk for AF and their closest genes including those coding for cardio-enriched TFs (reviewed in [3, 4, 5, 6]). Recently, a number of studies have demonstrated that cardiac GRNs are under the control of interleaved networks of regulatory non-coding RNAs (ncRNAs), which include microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). Mature miR transcripts (approximately 22-nucleotide long) act as inhibitors of target gene expression by either promoting mRNA degradation or suppressing translation. In this context, lncRNAs (more than 200 nucleotides long) can either activate or suppress gene expression by regulating chromatin conformation and TF binding or through sequestering miRNAs from their target mRNAs. Contemporary research has revealed that ncRNAs are dysregulated in many forms of adult heart disease in both patients and animal models [7, 8]. In particular, it was evidenced that ncRNAs may form additional critical layers of the intricate modulator architecture for the control of atrial gene expression [9, 10, 11, 12, 13, 14, 15].

This review broadly explores the gene regulatory mechanisms associated with susceptibility to AF providing key examples within the context of both cardiac TFs and ncRNAs. These two systems appear to have multiple levels of cross-regulation and act coordinately to achieve effective control of atrial rhythm effector gene expression. Perturbations of expression balance between TFs and ncRNA networks can promote AF development. In this context, several lines of evidence indicate that the TF-miRNA blueprint for AF susceptibility is distinct from that associated with chronic AF [16, 17]. Accordingly, the aim of the present review is to summarize the current evidence on the role of the cardiac TF-ncRNA co-regulatory networks in predisposition to AF. Deciphering the interplay between cardiac TFs and ncRNAs will likely lead to a more translational approach for preventing and treating AF.

Sources of atrial ectopic beats triggering fibrillation

Spontaneous self-terminating episodes of AF are one of the most common heart rhythm disorders. Ectopic pacemaking activity (i.e., electrical impulse generation outside the sino-atrial node (SAN)) and re-entry of excitation wavefronts are considered the most probable mechanisms involved in AF development. There is a substantial body of research demonstrating that erratic atrial premature beats can trigger AF in the presence of a vulnerable substrate. Once initiated, AF itself can lead to the so-called electric remodeling of atrial myocardium, which promotes fibrillation maintenance [1].

Focal triggering sites of spontaneous AF can reside in various anatomical structures such as the left atrial (LA) appendage as well as LA myocardial muscle extensions (“sleeves”) located in the pulmonary veins (PVs) (Fig. 1). The PVs are characterized by a unique myofiber architecture and electric properties that can lead to the ectopic activity that triggers AF, and PV ablation is widely used to terminate AF [18].

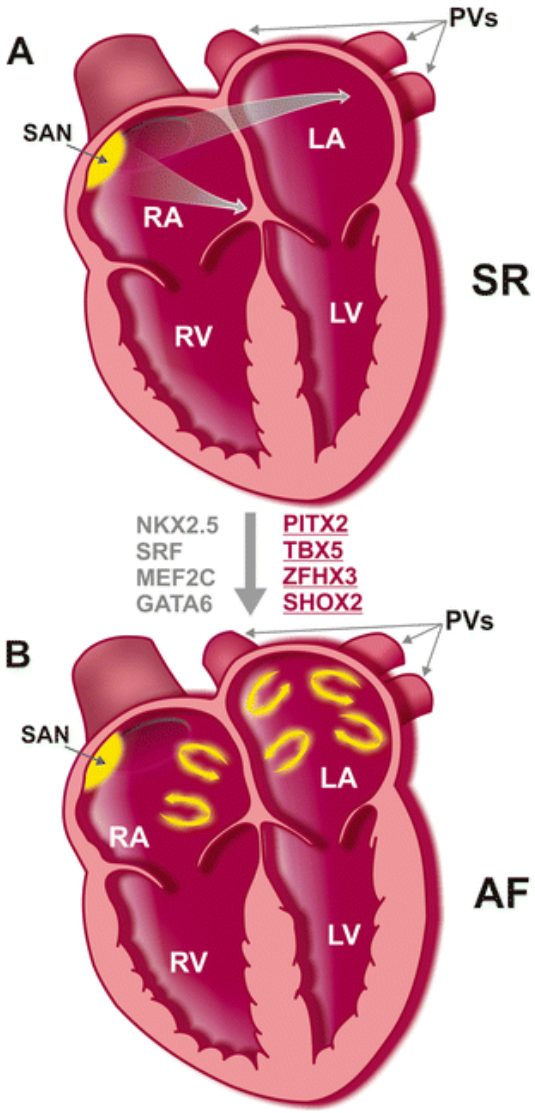

Fig. 1. Atrial activation patterns and transcription factors involved in the development of atrial fibrillation. **a** Normal atrial activation during sinus rhythm (SR). The sinus node (SAN) located at the entrance of the right superior cava vein in the right atrium (RA) generates electrical impulses which are distributed within large areas (big wide arrows) of the RA and left atrium (LA) to create normal rhythm. RV and LV right and left ventricles. **b** Atrial ectopic (non-SAN) rhythm activation. Ectopic pacemaking activity (semi-circular arrows) in the LA, pulmonary veins (PVs), or RA can trigger the development of atrial fibrillation (AF). Clinical studies have evidenced that more than 80% of the AF trigger impulses originate within PV muscular sleeves and LA muscles. NKX2.5, SRF, MEF2C, GATA-6, PITX2, TBX5, ZFHX3, and SHOX2 are the core cardiac TFs, which are thought to be responsible for initiation of AF. TFs implicated in susceptibility to AF by genetic and functional assays in animal models coupled with studies of samples from AF patients are marked in red, while those marked in gray have only sporadically been associated with an increased risk of AF. (Heart images taken from http://www.michiganmedicalreport.com/michigan_cardiology/details/241
/podcast.aspx, modified)

Some clinical data suggest that the right atrium (RA) could also play a role in AF triggering [19]. However, the LA and RA have different susceptibilities toward developing arrhythmias: LA arrhythmias are more frequently observed [20]. Atrial mapping in patients shows that paroxysmal AF may originate in the RA in no more than 20–25% of cases [21, 22].

In adult mice as well as in humans, the LA and RA differ in their gene expression patterns [23, 24, 25]. In this sense, some cardio-enriched TFs and miRNAs [26, 27] involved in the development and progression of AF demonstrating left-right asymmetry in their expression in atrial myocardium. Within the scope of this review, the expression patterns of several of such TFs and miRNAs in the human left and right atria are schematically outlined in Fig. 2.

Fig. 2. Schematic representation of transcription factors and microRNAs expression signatures in human left and right atria. The color intensity is proportional to relative differences in expression levels of the gene in the RA vs LA; lightly gray denotes a relatively low while black denotes a relatively high expression. RA right atrium, LA left atrium. Respective references are shown in brackets

In addition to interatrial ectopic pacemaking activities, pathophysiological cardiac conditions, such as heart failure, valvular heart disease, hypertrophic cardiomyopathy, acute myocardial infarction, and congenital heart disease, can lead to AF development. Intriguingly, it was recently found that accumulation of atrial adipose tissue is associated with AF [28]. Moreover, it was evidenced that human adult atrial epicardial cells differentiate into adipocytes [29] that, in turn, can contribute, under certain conditions [30], to the formation of AF substrate.

Transcription factors–microRNA co-regulation in atrial fibrillation

AF susceptibility is associated with rapid transcriptional remodeling of atrial myocardium. It is generally accepted that TFs and miRNAs jointly regulate target gene expression by either feed-forward or feedback mechanisms. However, the different roles of many TFs and miRNAs in the development of AF have been separately studied. In spite of such a mechanistic dissociation in the field of basic AF research, we will try to bring together the scattered findings on the atrial TF–miRNA circuits underlining AF susceptibility. The analysis of opposite correlations between TF and miRNA expression levels have allowed the identification of TF–miRNA regulatory circuits which are of particular interest in the context of atrial predisposition to AF development.

PITX2/miRNA circuits

PITX2 (pituitary homeobox 2 or paired-like homeodomain transcription factor 2), a member of the bicoid class of homeobox genes, is located within the human 4q25 AF-associated locus. In humans, the gene is transcribed into four distinct variants: *PITX2A*, *PITX2B*, *PITX2C*, and *PITX2D*. *PITX2C*, the predominant cardiac variant of the gene, is more highly expressed in the adult LA compared to RA [31, 32, 33]. *PITX2* has been extensively studied, particularly its functions in heart development. It is widely recognized that *PITX2C* implicated in multiple pathways of cardiac left–right (L–R) asymmetry [34, 35] also regulates L–R atrial identity. The phenotype of *PITX2C*-deficient mice is characterized by RA isomerism with two SANs at both right and left regions of sinoatrial junction, each expressing the same panel of SAN-specific molecular markers [36]. Of note, pediatric patients with RA isomerism, usually with two SANs, are characterized by a high incidence of AF [37]. There is growing evidence suggesting that *PITX2* plays a role in regulating gene expression as well as electrical, functional, and structural integrity in adult LA [38]. Of note, *PITX2* and *NKX2-5* control the development of LA myocardial "sleeves" in the PVs (see Fig. 1), the most frequent arrhythmogenic focus in patients with AF [39].

GWAS in humans revealed that genetic variants at chromosome 4q25 constitute the strongest locus associated with AF. Some of these 4q25 variants are located in the proximity of the *PITX2* gene suggesting that modulations of *PITX2* expression in atria are associated with susceptibility to AF development [40]. In this sense, CRISPR-Cas9-mediated editing of one of the AF-associated 4q25 variants proximal to *PITX2* in human stem cell-derived cardiomyocytes significantly downregulates *PITX2C* expression. This downregulation is most likely due to alteration of the TFAP2a (transcription factor AP-2 alpha) binding site(s) at the risk variant region that leads to inactivation of a putative *PITX2* enhancer [41].

Loss-of-function mutations in *PITX2* have been shown to be associated with familiar AF [42]. In addition, functional studies show that the mutation in the 5′ untranslated region of the *PITX2* gene, identified in probands with severe AF, leads to downregulation of this gene expression in atrial myocytes at both basal conditions and rapid pacing [43]. Data from animal models are well in line with these findings. In mice, *PITX2* haploinsufficiency predisposes to pacing-induced AF indicating that reduced *PITX2* levels promote an arrhythmogenic substrate as observed in different mouse models [31, 44, 45, 46]. In addition, unstressed adult *PITX2* mutant mice manifest electrocardiographic signs of sinus node dysfunction (SND) which is frequently associated with AF development in humans [47]. In this regard, it should be noted that the abnormal electrophysiological substrate for SND is localized in the RA while the majority of triggers and substrates for AF originate in the LA (see Fig. 1). Similarly to what has been observed in mice, there is an association between LA *PITX2* downregulation and increased atrial arrhythmogenicity in a rat experimental model of hypertension with spontaneous atrial arrhythmias [48]. In model

cell-based assays, *PITX2* knockdown significantly decreases the expression level of the *ZFHX3* TF which, in turn, may contribute to the occurrence of AF [49].While experimental data from animal models of *PITX2* knockdown do provide evidence that *PITX2* deficiency can play a role in susceptibility to AF, the results of transcriptomic profiling of atrial myocardium from patients with AF are not yet conclusive. Particularly, increased [50], decreased [45, 51], or unaltered [33] *PITX2C* levels were detected in atrial biopsy specimens from AF patients. *PITX2* modulates atrial resting membrane potential and alters the effectiveness of Na channel blockers; antiarrhythmic agents were found to be more effective in suppressing arrhythmias in atria with reduced *PITX2C* mRNA levels [52]. In humans, AF risk single-nucleotide polymorphisms (SNPs) are associated with increased *PITX2* expression [53]. These findings, taken together with the above data, indicate that the direct correlation between *PITX2* expression levels in the atrial myocardium and a multifactorial disorder like human AF remains elusive. (For more details, see the comment [54].)

PITX2 can contribute to regulation of atrial contractility and arrhythmogenesis through multiple pathways including a variety of ion channel, calcium handling, and gap junction proteins that are crucial for atrial pacemaker activity [38]. In addition, the analysis of cardiac expression of multiple miRNAs regulated by *PITX2* in the heart has yielded some interesting results in relation to the mechanisms by which *PITX2* may modulate several pathways leading to AF [2, 38]. *PITX2* expression is co-localized with the expression of miR-17-92 and miR-106b-25 clusters and loss of *PITX2* causes decreased expression of the corresponding miRNAs. Mice deficient in these miRNA clusters reveal characteristics similar to those of *PITX2* mutant mice, including a high predisposition to induced AF and dysregulation of *SHOX2* and *TBX3* expression [55].

Interestingly, when miRNA expression levels were found to either increase or decline during AF development [12, 56], they were likewise found to be modulated by *PITX2* as revealed in two distinct *PITX2* loss-of-function murine models that recapitulate some aspects of the human AF. Remarkably, expression of miR-21, which negatively regulates *PITX2* in atrial-derived cells [17], was downregulated in these mutant mice [46]. Of note, expression of miR-21 is upregulated in the LA of patients with long-term persistent AF as well as in a mouse model of spontaneous AF [12, 57, 58] and after short-term AF episodes in pigs; transfection of atrial cardiomyocytes with miR-21 mimic leads to *PITX2* downregulation [17]. In human patients, plasma levels of miR-21 significantly increased after AF ablation [59]. Together, these results highlight a possible reciprocal regulation between *PITX2* and miR-21 in various AF settings, although the actual mechanism by which they might form feed-forward/feedback loops to propagate their adverse effects on atrial myocardium is not well understood.

PITX2C was shown to negatively regulate the expression of miR-1 in the adult mouse LA [45]. When overexpressed in normal or infarcted rat hearts, miR-1 represses the expression of potassium channel subunits and connexins and thus provokes arrhythmogenesis [60]. In the porcine model of spontaneous self-terminating AF, induced ectopic tachyarrhythmia caused rapid downregulation of *PITX2C* which was inversely correlated with miR-1 upregulation in the LA of paced animals [17]. In contrast, expression of miR-1 is downregulated in patients with chronic persistent AF [61]. Several lines of experimental evidence suggest that *PITX2* also negatively regulates miR-29a expression in atrial myocardium [46, 62]. Importantly, a significant increase in the expression levels of miR-29a was observed in both LA [57] and RA [63] appendages from patients with chronic AF compared to those from the sinus rhythm controls. The calcium voltage-gated channel subunit alpha1C (*CACNA1C*) gene, playing an essential role in cardiac arrhythmogenesis, was identified as a target gene of miR-29a in atrial myocytes [63]. In this sense, it seems reasonable to suggest that suppression of aberrant activity of miR-29a by *PITX2* could ameliorate AF.

As in the case of miRNAs, lncRNAs could also be potent regulators of AF risk factors [64]. Recently, RNA sequencing of human LA/RA pairs identified an intergenic lncRNA named *PITX2* adjacent noncoding RNA (PANCR). Expression of PANCR positively correlates with *PITX2C* levels in human LA biopsy samples and PANCR may act as a positive regulator of *PITX2C*: PANCR knockdown represses *PITX2C* expression and in this regard mimics the consequences of *PITX2C* inactivation on mRNA and miRNA expression in differentiated cardiomyocytes [65].

Together, the data illustrate multiple levels of *PITX2* regulation, potentially requiring further investigations of any proposed causative association between *PITX2* expression levels in the human adult atria and the first clinically observable manifestations of a transient irregularity of the atrial rhythm.

TBX5/miRNA circuits

TBX5, a member of the Brachyury T-box TF family, is widely expressed in the human heart, including the atria [66]. *TBX5* undergoes extensive alternative splicing, generating several transcript variants encoding protein isoforms with different properties [67, 68]. Alteration of *TBX5* levels affects the expression of hundreds of genes, including genes implicated in AF pathogenesis [69, 70, 71].

The involvement of *TBX5* in human AF development was suggested through the analysis of the *TBX5* gain-of-function mutation in a large family of patients with mild Holt–Oram syndrome (HOS) and paroxysmal AF [72, 73]. However, *TBX5* loss-of-function mutations were found to be associated with a predisposition to the onset of AF in a subset of HOS patients [74]. Moreover, the *TBX5* loss-of-function mutation which decreases *TBX5* transcriptional activity was detected in patients with “lone” AF [75], suggesting that *TBX5* haploinsufficiency could contribute to AF development. In this regard, it was recently found that *TBX5*-knockout human cardiomyocytes are characterized by marked pro-arrhythmic activity [71].

The results of a number of GWAS analyses have linked intronic sequence variants of the*TBX5* gene to PR interval prolongation which is a surrogate AF risk marker in patients [76]. This is in line with growing evidence showing a strong association between several SNPs in the *TBX5* gene and lone AF in patients [68, 77]. Recent *cis*-expression quantitative trait locus analysis suggests that altered *TBX5* expression in the human LA plays a role in AF susceptibility [6].

Additional evidence linking *TBX5* and AF has emerged from studies in murine models. In mice, adult-specific *TBX5* deletion causes the rapid onset of AF affecting the expression of calcium-handling and other AF-susceptibility genes in atrial cardiomyocytes. In addition, it was found that *TBX5* directly activates *PITX2*, while *TBX5* and *PITX2* antagonistically regulate membrane effector genes. Most importantly, it has been demonstrated that *PITX2* suppression reverses the pro-arrhythmic effects of *TBX5* knockdown suggesting that deficiency of both, *TBX5* and *PITX2* could lead to the onset of AF, but through opposite mechanisms [78]. Interestingly, *PITX2* itself regulates the expression of *TBX5* in cardiomyocytes [79], and PITX2 insufficiency leads to molecular and electrophysiological impairment of calcium homeostasis in the mouse LA mediated by Wnt signaling genes and miRNAs [46].

Some studies have shown that miRNAs can act as essential components in *TBX5*-signaling networks at AF, through either regulation of their expression by *TBX5* or regulation of *TBX5* itself. In mouse cardiac cells and zebrafish embryos, *TBX5* was found to be able to regulate the expression of several miRNAs [80] and, in particular, miR-19 [81, 82]. MiR-19 expression levels are significantly increased in the LA of patients with paroxysmal AF [83]. In the mouse heart, miR-19 is transcribed as part of the miR-17-92 cluster which expression is positively regulated by *PITX2*. *TBX5* is a target gene of both miR-10a and miR-10b [84]. Expression of miR-10b was found to be upregulated in LA biopsies from patients with chronic AF and valvular heart disease [27] and miR-10b plasma levels are decreased in AF patients after catheter ablation [85]. In the porcine model, short-lasting atrial tachyarrhythmia was associated with significant upregulation of both miR-10a and miR-10b coupled with decreased *TBX5* expression in the LA of paced animals that may be permissive for AF development [17]. *TBX5*-dependent enhancer lncRNAs might also be functionally involved in *TBX5* regulated gene expression in atrial myocytes. Particularly, it was found that RYR2-associated *cis*-element RNA (RACER), a *TBX5*-dependent lncRNA, is required for expression of ryanodine receptor 2 (RYR2), the major calcium release channel on the sarcoplasmic reticulum in cardiomyocytes. As a whole, more than two thousand *TBX5*-dependent ncRNAs were identified in the mouse atria by deep sequencing [86].

Together, all these data indicate that alterations in *TBX5* expression levels in atrial myocardium may be a trigger for the production of the arrhythmogenic substrate.

ZFHX3/miRNA circuits

ZFHX3, the zinc finger homeobox 3 gene (formerly known as ATFB1), encodes a TF which was described as a transcriptional repressor for myogenic differentiation [87]. *ZFHX3* is highly expressed in the adult mouse heart [88] and human stem cell-derived cardiomyoblasts [89]. *ZFHX3* regulates transcription via direct interaction with predicted AT (adenine- and thymine-rich) motifs in the promoter region of target genes.

ZFHX3 located on the human chromosome 16q22 is one of the major AF susceptibility-conferring genes found by SNP scanning in Caucasian [90], European [91], Chinese [92], and Japanese [93] populations. Recently, gene-based association tests in AF patients linked single common genetic polymorphisms of the *ZFHX3* gene with different AF clinical phenotypes (paroxysmal and persistent AF), LA remodeling and, in turn, with AF recurrence after ablation [94, 95].

The results coming from in vitro cell-based assays show that *ZFHX3* can play an important role in AF predisposition and also support GWAS data on *ZFHX3* involvement in the genesis of human AF. It was found that tachypacing leads to *ZFHX3* downregulation in cultured atrial HL-1 myocytes. In turn, *ZFHX3* knockdown in HL-1 myocytes contributes to upregulation of mediators of inflammatory signaling [96] and deregulation of calcium homeostasis underlying increased atrial arrhythmogenesis [49].

There is growing evidence that *ZFHX3* molecular interactions with other AF-susceptibility genes, such as *PITX2* and *TBX5*, can markedly increase AF risk. In particular, experiments with both heart-irrelevant cell lines [97] as well as HL-1 atria-derived cells [46] revealed that silencing of *ZFHX3* expression significantly downregulates the expression of *PITX2C*. Conversely, overexpression of *ZFHX3* increased *PITX2C* expression. Remarkably, *ZFHX3* knockdown also significantly increased expression of *TBX5* [97].

ZFHX3 was predicted to be a downstream target gene of miR-1 and contains two miR-1 binding sites at its 3′-untranslated region; cell transfections with miR-1 mimics significantly decreased expression of *ZFHX3* at both mRNA and protein levels [97]. Reduced levels of miR-1 expression were found in human AF [61] suggesting this could lead to a certain degree of *ZFHX3* and *PITX2* upregulation in diseased atria, preventing, to some extent, further aggravation of AF.

SHOX2/miRNA circuits

SHOX2, the short stature homeobox 2 gene, encodes a TF which controls the development and function of SAN (the primary site for initiation and maintaining of the normal sinus rhythm) located in the adult RA (Fig. 1). The human *SHOX2* encodes two alternatively spliced transcripts. In a cardiac developmental context, *SHOX2* functions as a pro-pacemaker factor and antagonizes the *NKX2-5* activity in the PV myocardium (see Fig. 1) that is well known for its arrhythmogenic capacities [98, 99]. Transcriptome analysis did not reveal any significant differences in *SHOX2* expression levels between the LA and RA in sinus rhythm patients (see Fig. 2 and references therein).

Expression analysis revealed significantly reduced *SHOX2* transcript levels in RA samples from patients with early-onset AF. In addition, the miR-92b-5p was identified as a putative negative regulator of *SHOX2* expression in particular cohort of AF patients carrying a mutation in the 3′ untranslated region of the *SHOX2* gene [100]. However, the authors of this work investigated RA tissue, while AF normally originates in the LA. In mouse models, it was shown that *PITX2* which is highly expressed in the LA and PV myocardium negatively regulates *SHOX2* directly [44] or indirectly through upregulation of the miR-17-92/106b-25 cluster, that in turn represses *SHOX2*. Additionally, it was found that *SHOX2* upregulation in the fetal LA promotes LA ectopic automaticity [55]. It is therefore tempting to speculate that an imbalance between the expression dosages of *PITX2* and *SHOX2* in the LA and PV myocardium may lead to AF. In this context, it is likely that inhibitors of excessive expression of *SHOX2* in the LA could help prevent AF development.

Concluding remarks

Results of human AF GWAS screenings coupled with data from conditional gene manipulations in mice and cell-based functional assays identify a set of TF-miRNA co-regulatory loops as putative disease modules orchestrating susceptibility to induced or spontaneous AF. These modules include *PITX2*, *TBX5*, *ZFHX3*, and *SHOX2* TFs and their upstream and downstream miRNAs (Fig. 3). Previously, these TFs have either been implicated in cardiac development and differentiation or have been shown to be mutated in patients with different subtypes of AF. Notably, the association between these TFs is significant, implying not only a synergetic, but also a previously unrecognized opposite regulation of the expression of common downstream AF-associated genes [78]. Remarkably, there is a growing evidence suggesting that other cardiac TFs, such as *NKX2-5*, *SRF*, and *GATA-6*, may be associated with or responsible for early-onset human AF [16, 101, 102, 103].

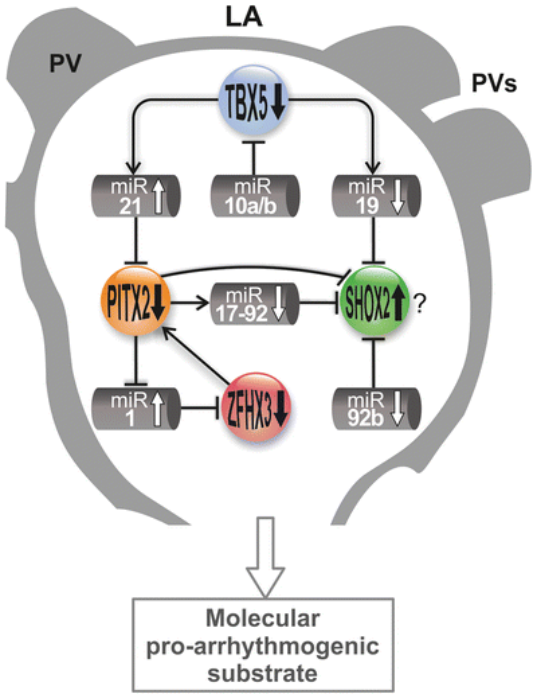

Fig. 3. Cardiac transcription factors and related microRNAs that are known or suggested to be involved in the initiation of AF. AF susceptibility, as functionally validated using in vitro and in vivo models, is associated with deregulated expression of transcription factors (PITX2, TBX5, ZFHX3, and SHOX2) and related miRNAs (miR-21, miR-19, miR-17-92, and miR-92b). Bold arrows (black/white) denote either up or down expression of the genes. The question mark represents a speculative assertion that SHOX2 upregulation in the LA or PV myocardium might promote ectopic automaticity. Whether miR-10a and miR-10b are directly involved in AF predisposition remains to be experimentally determined. Of note, the miR-17–92 miRNA cluster generates a single polycistronic primary transcript that yields six mature miRNAs: miR-17, miR-18a, miR-19a, miR-19b, miR-20a, and miR-92a [107]. LA left atrium, PVs pulmonary veins

Could studies of atrial-associated TF-miRNA modules identify novel therapeutic targets and help to develop novel treatment strategies for the primary prevention of AF development or AF recurrence? Within each described module, a dynamic expression balance between TFs and miRNAs may have a certain clinical relevance as it was found that a low activity of *PITX2*, *TBX5*, and, probably, *ZFHX3* can lead to or be associated with irregular ectopic atrial activity. In the porcine model of transitory AF, short-term atrial pacing resulted in significant upregulation of miR-21 and miR-10a/b which was associated with the downregulation of their respective target TFs, *PITX2*, and *TBX5* [17]. In this respect, antagomiR-induced knockdown of miR-21 and miR-10a/b might be a means to prevent recurrence of AF paroxysms. However, future studies directed at an in-depth understanding of the pathways regulated by atrial TF-miRNA circuits in various AF settings are necessary before translational treatment strategies can be considered.

Besides the role as putative therapeutic targets, the cardiac-enriched nc-RNAs discussed in the present review may be employed as prognostic and diagnostic biomarkers in AF. Indeed, it is increasingly recognized that circulating plasma miRNAs could be promising biomarkers for risk stratification in AF patients [12, 104]. In particular, plasma levels of two *PITX2*-associated miR partners, miR-1 and miR-21, are decreased in patients with sustained atrial tachycardia [105] and paroxysmal AF [59, 106], respectively. In contrast to miRNAs, the profiling of circulating lncRNAs is only starting to emerge as a putative biomarker tool for heart disease.

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Compliance with ethical standards

Conflict of interest
The authors declare that they have no conflicts of interest.

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