18 Non-coding RNA and Cardiac Electrophysiological Disorders

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Abstract

Cardiac arrhythmias are common diseases affecting millions of people worldwide. A broad and diverse array of arrhythmias exists, ranging from harmless ones such as sinus arrhythmia to fatal disorders such as ventricular fibrillation. The underlying pathophysiology of arrhythmogenesis is complex and still not fully understood. Since their discovery, non-coding RNAs (ncRNAs) and especially microRNAs (miRNAs) came into the spotlight of arrhythmia research as it has been shown that they play an important role in regulating normal development of the cardiac conduction system and are involved in remodeling processes leading to arrhythmias. This chapter will give a brief overview on basic electrophysiologic concepts and will summarize the current knowledge on ncRNAs and their role in arrhythmogenesis.

Keywords

Non-coding RNA · Cardiac electrophysiology · Arrhythmia · Arrhythmogenesis · Remodeling · Reentry · Conduction

1 Background

Cardiac arrhythmias are common resulting in significant morbidity and mortality. Especially ventricular arrhythmias are a major cause for cardiovascular death in the context of ischemic heart failure (HF) or myocardial infarction [1].

A vast variety of structural changes (e.g. fibrosis, dilatation or inflammation) as well as changes in ion channel function or expression, alterations of the calcium homeostasis or neurohormonal dysregulation can lead to the onset and perpetuation of arrhythmias [1]. Those mechanisms are called 'proarrhythmic remodeling' and are induced by various triggers such as ischemia or pressure overload. On a cellular level these remodeling processes are regulated by numerous mediators such as non-coding RNAs. Non-coding RNAs (ncRNAs) are small RNA molecules that are not translated into proteins [2]. They are able to regulate gene expression on different levels

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This chapter will summarize the research progress on non-coding RNAs and their role in cardiac electrophysiology other than atrial fibrillation that will be discussed in the following chapter.

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like transcriptional modulation (e.g. by inhibiting expression of enhancers/repressors), epigenetic targeting (e.g. by affecting expression of enzymes involved in histone formation) or post transcriptional regulation (e.g. by mediating degradation of already transcribed target genes) [3]. When it comes to cardiac arrhythmias, research has focused on microRNAs (miRNAs) rather than other non-coding RNAs since they have been demonstrated as key regulators in electrical and structural remodeling of the heart [4, 5]. The underlying electrophysiological alterations leading to cardiac arrhythmias are various and often categorized as disorders of impulse formation or impulse conduction caused by complex processes summarized under the term proarrhythmic 'remodeling' consisting of structural and electrical remodeling [6, 7].

In recognition of the evidence currently available, this chapter will focus on microRNAs and give an outlook to other ncRNAs if there is evidence available.

1.1 Basics of Cardiac Conduction

In order to maintain sinus rhythm cardiac conduction system cells and the working myocardium are strictly orchestrated and require a perfect coordination of excitation, conduction, refractoriness and electromechanical coupling [1]. Any change in this fragile equilibrium may cause the occurrence of arrhythmias.

Under physiologic conditions a characteristic sequence of voltage changes driven by de- and repolarizing currents leads to the generation of the cardiac action potential. Cardiomyocytes normally display a resting membrane potential of −80 mV [7]. The electrical activity relies on different ion currents through various transmembrane-proteins – the so-called ion channels. Among them are Na^+, Ca^{2+}, and K^+ channels which contribute to the cardiac action potential by opening and closing at different time points [1]. The cardiac action potential is divided into different phases: first, the initial rapid depolarization driven mainly by voltage gated sodium channels; second, a long plateau phase driven mainly by an equilibrium between calcium and potassium currents; third, the repolarization driven by inward potassium currents, and fourth, the resting period when the cardiomyocyte comes back to its resting membrane potential [1, 8, 9].

A physiologic heartbeat begins with a spontaneous depolarization in a small atrial area, the so called sinus node. The sinus node myocytes are specialized and vary from other myocytes by their spontaneous depolarizations driven by a sodium current. After excitation of the atria the impulse reaches the atrioventricular node which electrically separates the atria from the ventricles. It then continues through the his bundle which divides into two branches, the left and the right bundle branch. These branches then taper out producing countless Purkinje fibers which finally reach the myocytes of the ventricles, distributing the electrical excitation among all myocytes.

1.2 Common Proarrhythmogenic Changes

Common changes favoring arrhythmia affect each part of physiologic excitation starting with the impulse formation. The ability of the sinus node (or other subsidiary pacemaker cells) to spontaneously generate electrical impulses is called 'automaticity'. Alterations of the gene expression in the sinus node, for example in heart failure, may lead to an enhanced automaticity that in turn may result in sinus tachycardia. Under normal conditions impulse formation takes place within the sinus node. If cells outside the sinus node reach their threshold potential before they are reached by a sinus impulse, so called ectopy occurs that may potentially lead to arrhythmias [7]. The most important mechanisms underlying ectopy are early and delayed afterdepolarisations due to imbalances in the calcium homeostasis [10]. Especially early afterdepolarisations are common in ventricular myocardium and are associated with ventricular arrhythmias such as long QT syndrome [11].

Another major cause for cardiac arrhythmias are changes favoring atrial or ventricular reentry by affecting the impulse conduction. Physiologically, a refractory period follows each excitation, making the cardiomyocyte resistant to premature electrical impulses and guaranteeing that only physiologic impulses from the sinus node can cause depolarizations. The cardiac refractoriness ultimately depends on the action potential duration (APD), meaning that all changes to APD may favor arrhythmias. Changes leading to slowed electrical conduction or a shortened refractory period can lead to a situation where a premature electrical impulse reaches cardiomyocytes that are already excitable (e.g. because the physiologic impulse from the sinus node is slow and has not reached the cardiomyocyte yet or the cardiomyocyte's repolarization is fastened) and will be conducted (which makes the cardiomyocytes refractory against physiologic impulses from the sinus node) establishing a 'reentry' circuit that can lead to atrial or ventricular (tachy-)arrhythmias [10]. Conduction velocity mainly depends on sodium channels, gap junctions and cardiac tissue structure [10]. For example in heart failure changes to cardiac ultrastructure like fibrosis favor reentry by altering conduction velocity [12].

Ion channel dysfunctions resulting from altered ion channel gene expression or function (so called channelopathies) following various triggers such as ischemia or genetic mutations often underly the phenomena described above [13].

2 MicroRNAs Described in Cardiac Arrhythmia

This section will provide a brief overview on miRNAs involved in cardiac arrhythmogenesis, purposely excluding atrial fibrillation, which will be discussed in Chap. 19. Figure 18.1 illustrates the interaction between miRNAs and their target genes, and Table 18.1 provides an overview of the miRNAs described in this section.

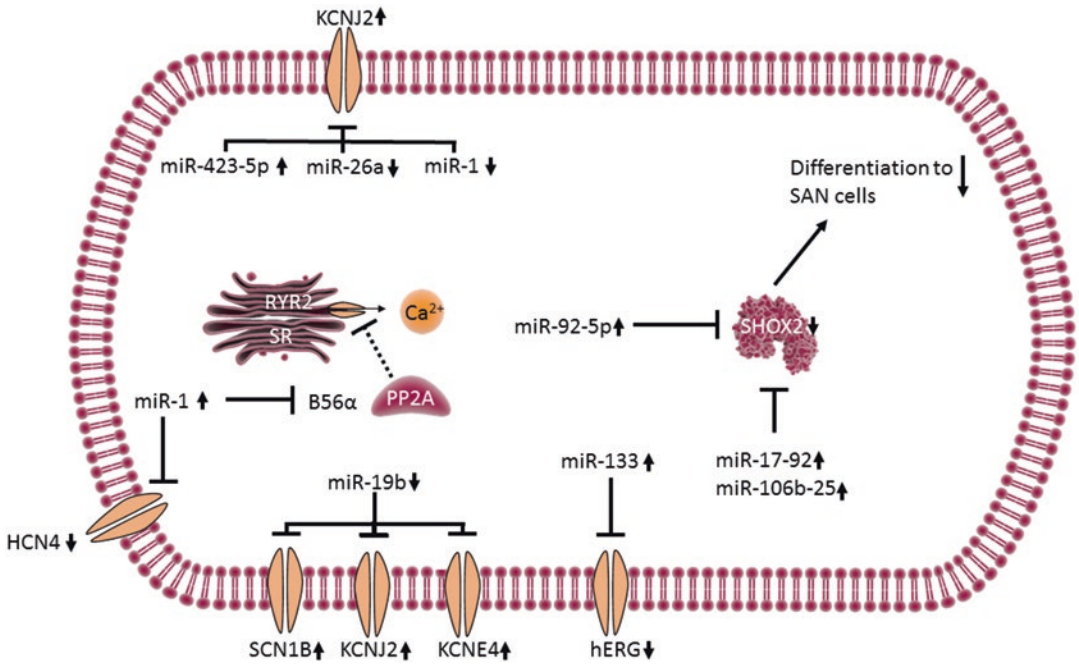

Fig. 18.1 Regulation of miRNAs involved in arrhythmogenesis and their respective targets

Table 18.1 Overview of microRNAs involved in the genesis of arrhythmias

Non-coding RNA	Regulation in disease	Mechanism	Species	Entity	References
miR-1	Downregulated	Upregulation of Kir2.1 potassium channel	Rat	SSS	[36]
miR-1	Upregulated	Downregulation of *HCN4*	Mouse	Sinus bradycardia	[16]
miR-19b	Downregulated	Upregulation of various sodium- and potassium channels; prolongation of APD	Zebrafish	AV- Block	[19]
miR-26a	Downregulated	Upregulation of *KCNJ2*	Dog	Heart failure	[22]
miR-30	Downregulated	CTGF mediated induction of fibrosis	Rat	Heart failure	[21]
miR-92b-5p	Upregulated	Repression of *SHOX2*	Mouse	SSS	[25]
			Human		
miR-133	Upregulated	Repression of hERG (reduced potassium current I_{Kr})	Dog	Myocardial fibrosis	[20]
miR-17-92 & miR-106b-25	Downregulated	Alteration in cardiomyocyte differentiation	Mouse	SSS	[24]
miR-423-5p	Upregulated	Downregulation of *HCN4*	Mouse	Sinus bradycardia	[37]

2.1 miR-1

The first link between cardiac arrhythmias and miRNA was made by Yang et al. in 2007. They were able to show a dysregulation of miR-1 (overexpression) in a rat model of acute myocardial infarction leading to altered Ca^{2+} handling and thus, arrhythmias. Elimination of miR-1 was able to rescue the phenotype [14]. Further investigation revealed two miR-1 target genes: *GJA1*, which encodes connexin 43 (Cx43) that is one of the major gap junctions mediating the electrical conduction from cell to cell and *KCNJ2*, which encodes the potassium channel subunit Kir2.1 that is critical for establishing the resting membrane potential. Repression of these two proteins by miR-1 leads to a slowed conduction and a more depolarized resting membrane potential (seen as QRS complex widening and increased resting membrane potential in this model) thus potentially favoring cardiac arrhythmias [14]. A further role for miR-1 in cardiac arrhythmogenesis has been described by Terentyev et al. in 2009. They showed an increase in the amplitude of inward calcium current leading to increased excitation, elevated diastolic calcium leak from the sarcoplasmatic reticulum and reduced sarcoplasmatic reticulum calcium content, all potentially favoring arrhythmias in general [15]. The miRNA represses the Protein phosphatase 2 (*PP2A*) in this mode of action. These data were all not linked to a particular arrhythmia and describe general effects of miR-1 on the myocardial electrophysiology. Interestingly, miR-1 was also found to have an inhibitory effect on the expression of *HCN4* resulting in sinus bradycardia as an adaption to exercise training [16]. Fittingly, miR-1 was described to be upregulated in the blood of Marathon runners after running a marathon [17]. This miRNAs expression level also correlated with the diameter of the left atrium in elite runners, suggesting a potential use as a biomarker for atrial remodeling [18].

2.2 miR-19b

There is also some data available on the influence of miR-19b on the action potential duration (APD) in zebrafish. This miRNA exhibits an inhibitory effect on the expression of various sodium and potassium channels, thus prolonging the APD. Zebrafish lacking miR-19b presented

bradycardia due to AV block with concomitant loss of contractile function [19].

2.3 miR-133

miR-133 has been shown to affect the QT interval. Shan and colleagues were able to demonstrate that upregulation of miR-133 in a dog tachypacing model led to decreased protein levels of hERG (a potassium channel subunit of the delayed rectifier potassium current I_{Kr}) and subsequently to prolonged QTc interval and increased mortality rates. The effect could be rescued by blocking miR-133 with an antisense inhibitor, thus proving a role for miR-133 in long QT syndrome [20].

2.4 miR-30

In a transgenic rat model of hypertension-induced heart failure downregulation of miR-30 has been shown to be associated with increased fibrosis via CTGF mediated induction of extracellular matrix protein expression [21]. This may lead to a proarrhythmogenic substrate, a link to a specific arrhythmia, however, was not demonstrated in this study.

2.5 miR-26a

In a dog model of chronic heart failure induced by atrial tachypacing miR-26 was significantly downregulated followed by an upregulation of its target gene *KCNJ2* and consecutive action potential shortening favoring reentry [22]. The authors linked this miRNA to atrial arrhythmias.

2.6 miR-17-92 and miR-106b-25

Sick sinus syndrome marks an important entity regarding both healthcare costs as well as patient morbidity since it is responsible for the vast majority of pacemaker implantations [23]. Recent studies have shown miR-17-92 and miR-106b-25 to be involved in the pathogenesis of sick sinus syndrome [24]. Regulated by *Pitx2* – a transcription factor – they directly target genes (*Shox2* and *Tbx3*) involved in the differentiation of cardiomyocytes into cells forming the sinus node (so called nodal cells). If those miRNAs are knocked out, the threshold for pacing induced atrial fibrillation in mice decreases significantly [24]. The same researchers were able to show that cardiac specific knockout of miR-17-92 alongside with haplotype insufficiency of miR-106b-25 leads to sinus node dysfunction and second degree atrioventricular block in mice [24].

2.7 miR-92b-5p

Strikingly, miR-92b-5p was found to act inhibitory in the same pathway as miR-17-92 and miR-106b-25 in mice and is dysregulated in the blood of patients with atrial fibrillation [25]. Mechanistically, a variant (c.∗28 T > C) in the 3'UTR of the gene *Shox2* creates a functional binding site for this miRNA in patients with early onset atrial fibrillation. These results were validated in phenotypic rescue experiments in zebrafish. This group could also show that the expression of *Shox2* is significantly reduced in the right atrial appendages of atrial fibrillation patients.

2.8 miR-423-5p

The hearts of athletes react to repeated endurance training with an adaptive contractile and electrophysiological remodeling leading to sinus bradycardia. For instance, miR-423-5p was recently shown to be pivotal in the processes leading to sinus bradycardia by targeting *HCN4*, an ion channel responsible for the so called funny current in the sinus node [37]. Fittingly, knockdown of miR-423-5p reversed this training-induced bradycardia via normalization of HCN4 expression levels and establishing a regular funny current. Since these effects were elucidated in swim-trained mice, a similar mechanism in human athletes remains only speculative.

3 Long Non-coding RNAs Involved in the Development of Cardiac Arrhythmia

Since other ncRNAs, such as long non-coding RNAs (lncRNAs), only recently shifted into the spotlight of cardiovascular research there is only limited data available on their role in cardiac arrhythmogenesis. This section will provide a brief look into lncRNAs demonstrated as mediators in cardiac arrhythmias. Several lncRNAs have been described in cardiovascular disease (for example AK048451 (CHRF), myocardial infarction associated transcript (MIAT) or AK017121 (CARL)) which lead to cardiac hypertrophy, or interfere with cardiac apoptosis in ischemia/reperfusion injuries [26]. These are processes possibly triggering arrhythmias, and there are already some studies available proofing a link between lncRNA dysregulation and various arrhythmias. Table 18.2 shows a summary of the lncRNAs mentioned in this section.

3.1 Kcnq1ot1

Long QT syndrome can be caused by mutations in the gene *KCNQ1* [27]. Recent data has shown that the expression of *KCNQ1* can be inversely repressed in cis by Kcnq1ot1, a lncRNA produced from the introns of its gene. It has been shown that KCnq1ot1 loses its imprinting throughout the process of cardiac development leading to transcription, which then affects the expression of *KCNQ1* in differentiated cardiomyocytes rather than during early heart development [28, 29].

3.2 Cardiac Conduction Regulatory RNA (CCRR)

The remodeling processes in heart failure (HF) can lead to an enhanced arrhythmogenicity of the myocardium. Only recently, Zhang et al. established CCRR as an antiarrhythmic lncRNA in both mice and humans with HF. This lncRNA acts via preventing the degradation of Cx43, thus improving cardiac conduction. Knockdown of CCRR lead to a destruction of intercalated discs and gap junctions resulting in electrical conduction slowing, an effect similar to adverse cardiac remodeling seen in HF [30].

3.3 ZFAS1

As described above, calcium handling is one of the key factors in electromechanical coupling, with any disturbance potentially causing arrhythmias. ZFAS1 is a lncRNA reported to directly inhibit SERCA by suppressing its ATPase function, impairing cardiac contractility and favoring arrhythmias [31].

3.4 GAS5

The lncRNA GAS5 has been described to interact with miR-21 leading to hampered activation of cardiac fibroblasts via miR-21 upregulation in TGF-beta1 activated cardiac fibroblasts and subsequent lowered levels of *COL1A1*, *alpha-SMA* and *PTEN*. This indicates a role for GAS5 in the development of cardiac fibrosis, one major structural contributor to cardiac arrhythmias [32].

3.5 Kcna2 Antisense RNA (Kcna2 AS)

HF often triggers ventricular arrhythmias. Underlying mechanisms include APD prolongation due to decreased potassium currents (e.g. I_{Ks}). This was shown to be regulated by Kcna2, which in turn can be repressed by Kcna2 AS. In rats with congestive HF, the ventricular Kcna2 AS expression increases and the animals present a higher incidence of ventricular arrhythmias because of a prolonged APD [33].

3.6 TCONS_00075467

Knockout of TCONS_00075467 in rabbits lead to a shortened atrial effective refractory period

Table 18.2 Overview of lncRNAs involved in the genesis of arrhythmias

Non-coding RNA	Regulation in disease	Mechanism	Species	Entity	References
Kcnq1ot1	Upregulated	Downregulation of *KCNQ1*	Human	Long QT- Syndrome	[27–29]
Cardiac conduction regulatory RNA (CCRR)	Downregulated	Destruction of intercalated discs and gap junctions	Mouse	Heart failure	[30]
Kcna2 antisense RNA (Kcna2 AS)	Upregulated	Reduced IKs and prolongation of APD	Rat	Heart failure/ventricular Arrhythmias	[33]
Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)	Upregulated	Downregulation of I_{to}	Rat	Myocardial ischemia	[35]
GAS5	Downregulated	Increased fibrosis	Rat	Heart failure	[32]
TCONS_00075467	Downregulated	Shortened APD, lowered L-type Ca^{2+} current density	Rabbit	Heart failure	[34]
ZFAS1	Upregulated	Direct SERCA2a-inhibition	Mouse	Myocardial ischemia	[31]

(AERP), shortened action potential as well as lowered L-type calcium current density through sponging miR-328 in atrial myocytes favoring arrhythmia [34].

3.7 Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

MALAT1 is highly abundant in the heart after myocardial ischemia. Downregulation of this transcript induces an increased expression level of Kv4.2 and Kv4.3, transient outward potassium current (I_{to}) and peak current density [35]. This suggests a potential link to cardiac arrhythmias, which needs to be elucidated by other studies.

4 Summary

To put it in a nutshell, a growing body of evidence suggests that microRNAs are crucial factors regulating both normal cardiac electrophysiology and the occurrence of arrhythmias. Mechanistically, an altered microRNA expression mostly triggers a different pattern of ion channels changing the electrophysiological properties of the cardiomyocytes. The role of other non-coding RNAs, such as lncRNAs, in arrythmogenesis are still more elusive today. Some lncRNAs could directly be linked to tachyarrhythmias, while there is no evidence on an involvement of lncRNAs in the genesis of bradyarrhythmias. In addition, no evidence could be found for an entanglement of other classes of non-coding RNAs in arrhythmogenesis yet.

All in all, non-coding RNAs are involved in the pathophysiology of arrhythmias and might therefore serve as targets for the development of innovative novel drugs that may allow to treat cardiac arrhythmias in a causal fashion in the future.

Competing Financial Interests The authors declare no competing financial interests.

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