NcRNAs in Cardiac Action Potential

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microRNAs represent the most studied type of small ncRNAs and it has been demonstrated that miRNAs play essential roles in multiple biological contexts, including normal development and diseases. Cardiac arrhythmias are prevalent among humans across all age ranges, affecting millions of people worldwide. While cardiac arrhythmias vary widely in their clinical presentation, they possess shared complex electrophysiologic properties at cellular level that have not been fully studied.

Keywords: cardiac arrhythmia ; microRNAs ; lncRNAs ; cardiac action potential

1. The Electrical Components of the Adult Heart

Rhythmic contraction of the heart, leading to alternative systole and diastole contraction phases is controlled by the cardiac conduction system (CCS). The CCS is formed by slow and fast conduction pathways. The slow components are two distinct low conducting and self-firing nodes, the sinoatrial and the atrioventricular node, respectively. The sinoatrial node is located at the junction between the right superior caval vein entrance and the atrial chamber myocardium and is the main pacemaker of the heart [1]. The atrioventricular node is located at the top of the interventricular septum just at the junction between atrial and ventricular myocardium. The fast conducting components of the cardiac conduction system are exclusively located in the ventricular chambers, and are composed by the bundle of His, the left and right bundle branches, and the Purkinje fiber network [1].

At cellular level, the electrical activity of the myocardial cells is governed by an exquisite balance of inward and outward ion currents that configure the cardiac action potential. The cardiac action potential can be divided in at least four different phases. The first phase is initiated with a rapid upstroke of inward sodium currents, leading to the depolarization phase. Subsequently, the repolarization phase is initiated with fine-tuned balance of outward potassium currents, leading to phases two (ITO currents) and three (IK currents) of the cardiac action potential to finally reach the fourth phase of resting membrane potential (IK1 currents) [2][3][4]. During the plateau phase, calcium contraction coupling also takes place, by the activation of the ICa,L currents followed by mobilization of intracellular calcium from the sarcoplasmic reticulum, throughout the calcium-induced calcium release mechanism [5][6][7]. This general configuration of the cardiac action potential, although applicable to all cardiomyocytes, displays subtle variations on distinct cardiac regions. Importantly, such variability is due to distinct molecular substrates governing such events, such as for example, the upstroke phase in the cardiac action potential of the cardiac conduction system is governed by cation channels, with limited contribution of the sodium channels [3][4]. In addition to the distinct functional properties of the cardiac conduction system, the working myocardium also display significant differences between each cardiac regions—e.g., between atrial and ventricular myocardium—and also within the ventricular myocardium itself—e.g., epicardial vs. endocardial configurations. Such regional differences are mainly motivated by regional differences in the relative contribution of the outward potassium channels governing the rapid (ITO; IKur), plateau (IKr; IKs), and final (IKs; IK1) phases of the cardiac action potential repolarization as well as by the L-type calcium channels in the plateau phase. Finally, it is important to highlight that there are notable species-specific differences in the contribution of the discrete ion currents to the final configuration of the cardiac action potential. Such differences are particularly applicable to the repolarization phase in distinct experimental models such as rat, mouse, pig, and zebrafish as compare to humans, as widely documented elsewhere [8][9][10][11][12][13][14].

2. Role of ncRNAs in the Cardiac Action Potential

2.1. ncRNAs in the Upstroke Phase (INa Currents)

The upstroke phase of the cardiac action potential in fast conducting cells, i.e., atrial and ventricular myocytes, is primarily modulated by the fast INa current (NaV1.5) with a smaller contribution of Nav1.8. Importantly, the function of the pore-forming Nav1.5 channel is also modulated by ancillary subunits such as Navβ1-Navβ4 (**Figure 1**A). SCN5A encodes the

voltage-gated Na+ channel NaV1.5. Mutations in SCN5A are associated to inherited arrhythmias and cardiomyopathy [15][16][17][18]. Moreover, single-nucleotide polymorphisms (SNPs) linked to SCN5A splicing, localization, and function are also associated to sudden cardiac death [19][20]. SCN10A encodes the voltage-gated Na+ channel NaV1.8. Importantly, mutations in SCN10A have also been linked to sudden unexplained death [21], atrial fibrillation [22][23], and Brugada syndrome [20][24][25]. Furthermore, SCN5A and SCN10A share common regulatory elements that are relevant for cardiac function [26].

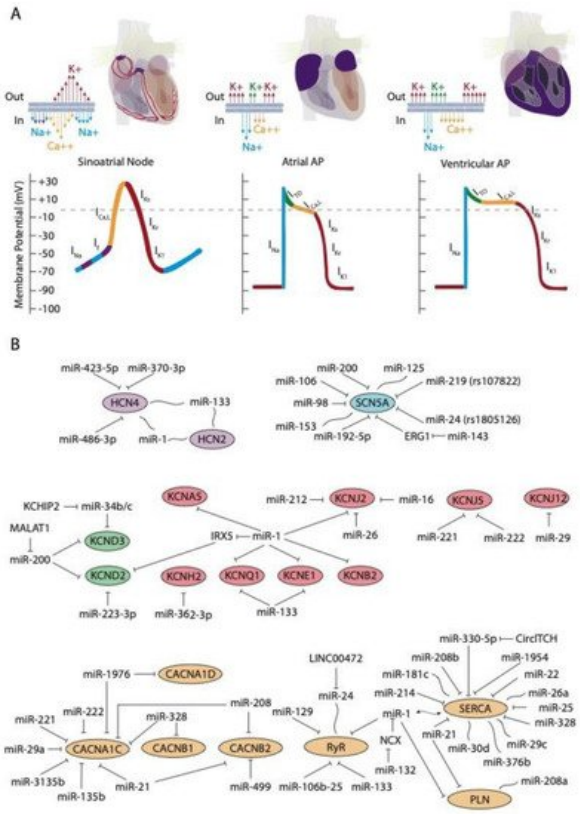

Figure 1. (**A**) Graphical representation of the cardiac action potential in the sinoatrial node (and also the atrioventricular node) and in contractile working myocardium of the atrial and ventricular chambers. (**B**) Schematic representation of the functional roles ncRNAs within the cardiac action potential regulation (— direct; ∼ indirect). Colors represent different phases of the cardiac action potential and related genes.

Similarly, the impact of microRNAs in the slow component of the INa current, governed by SCN10A pore-forming channel has not been reported in the cardiovascular context, although some evidences have been reported in other biological contexts such as pain development [27][28]. A summary of the microRNA interaction with the sodium channels is provided on **Table 1**, while their links to distinct cardiac diseases is provided on **Table 2**.

Table 1. List of microRNAs reported to modulate ion channel expression in the heart.

Current	microRNA	Gene	Function	Reference
INa	miR-98, miR-106, miR-200, miR-219, miR-125, miR-153	SCN5A	INa ↑/INa ↓	[29][30]
	miR-192-5p		INa ↓	[31]
	miR-200c		-	[32]
	miR-143		INa ↓	[33]
	miR-24		INa ↓	[34]
If	miR-423-5p	HCN4	If ↓	[35]
	miR-370-3p		If ↓	[36]
	miR-486-3p		If ↓	[37]
	miR-1, miR-133		If ↑	[38][39][40][41]
	miR-1, miR-133	HCN2	If ↑	[38][39][40][41]

Current	microRNA	Gene	Function	Reference
ITO	miR-1	KCND2	ITO ↓	[42]
	miR-223-3p		ITO ↓	[43]
	miR-34b/c		ITO =	[44]
	miR-200		ITO ↓	[45]
	miR-200	KCND3	ITO ↓	[45]
IKur	miR-1	KCNA5	IKur ?	[46]
IKr	miR-134, miR-103a-1, miR-143, miR-3619	hERG	IKr ↓	[47]
IKS	miR-1, miR-133	KCNE1	IKS ↓	[48][49]
	miR-1, miR-133	KCNQ1	IKS ↓	[48]
	miR-1, miR-133	KCNB2	IKS ↓	[49]
IK1	miR-1	KCNJ2	IK1 ↓/IK1 ↑	[50][51][52]
	miR-16		IK1 ↓	[53]
	miR-26		IK1 ↑	[54][55]
	miR-212		IK1 ↓	[56][57]
	miR-29	KCNJ12	IK1 ↓	[58]
	miR-221/222	KCNJ5	IK1 ↓	[59]
ICa,L	miR-328	CACNA1C	ICa,L ↓	[60]
	miR-21, miR-208b		ICa,L ↓	[61][62]
	miR-20a, miR-3135b		ICa,L ↓	[63]
	miR-499		ICa,L ↓	[64]
	miR-135b		ICa,L ↓	[65]
	miR-221/222		ICa,L ↓	[59]
	miR-328	CACNB1	ICa,L ↓	[60]
	miR-21, miR-208b		ICa,L ↓	[61][62]
	miR-499	CACNB2	ICa,L ↓	[64]
	miR-329		ICa,L ↓	[64]

Current	microRNA	Gene	Function	Reference
CICR	miR-106b	RYR2	-	[66][67]
	miR-129			[68]
	miR-1, miR-133			[69][70]
	miR-23	SERCA2A	-	[71][72]
	miR-25			[73][74]
	miR-328			[75][76]
	miR-29c			[77]
	miR-21			[78]
	miR-208b			[62]
	miR-22			[79]
	miR-214			[80]
	miR-1954			[81]
	miR-376b, miR-1, miR-26a, miR-30d, miR-181			[82]
	miR-1, miR-21	PLN	-	[83]
	miR-208a			[84]
	miR-132	NCX1	-	[85]
	miR-1			[80]

Table 2. List of genes involved in the cardiac action potential, their link to cardiovascular physiopathological conditions and their functional alterations in relation to distinct microRNAs signatures observed therein.

Gene	Disease	Alteration	Mir Related	Reference
SCN5A	Inherited arrhythmias and cardiomyopathy	Mutation	-	[15][16][17][18]
	Sudden death	SNPs	-	[19][20]
	Brugada syndrome	SNPs/↓ expression	miR-219	[29][30]
	Atrial fibrillation	↓ expression	miR-192-5p	[31]
	Heart failure	SNPs/↓ expression	miR-24	[34]
SCN10A	Sudden death	Mutation	-	[21]
	Atrial fibrillation		-	[22][23]
	Brugada syndrome		-	[86][24][25]
HCN4	Bradycardia	↓ expression	miR-423-5p, miR-370-3p	[35][36]
	Age atrial fibrillation	↑ expression	miR-1, miR-133	[38]
	Myocarial infarction	↑ expression	miR-1, miR-133	[39][40]
HCN2	Age atrial fibrillation	↑ expression	miR-1, miR-133	[38]
	Myocardial infarction	↑ expression	miR-1, miR-133	[39][40]
KCND2	Sudden death	↓ expression	miR-1	[42]
	Acute myocardial infarction	↓ expression	miR-223-3p	[43]
	Myocardial infarction	↓ expression	miR-200c	[45]

Gene	Disease	Alteration	Mir Related	Reference
KCNH2	LQT syndrome (type 2)	Mutation	-	[87]
	Heart failure	↓ expression	miR362-3p	[88]
KCNE2				
LQT syndrome (type 6)				
LQT syndrome (type 1)	LQT syndrome (type 1)	↓ expression	-	[89][90][91]
	Atrial fibrillation	↓ expression	miR-1	[49]
KCNB2				
Atrial fibrillation	Myocardial infarction	↓/↑ expression	miR-1, miR-16	[51][54]
	Atrial fibrillation	↑ expression	miR-1, miR-26	[50][52][55]
	Heart failure	↓ expression	miR-212	[57]
KCNJ12	Myocardial infarction	↓ expression	miR-29	[58]
KCNJ5	Atrial fibrillation	↓ expression	miR-221/222	[59]
CACNA1C	Atrial fibrillation	↓ expression	miR-221/222	[59]
			miR-328	[60]
			miR-21	[61]
			miR-208b	[62]
			miR-29b, miR-3135b	[63]
CACNB2	Atrial fibrillation	↓ expression	miR-21	[61]
			miR-208b	[62]
			miR-499, miR-329	[64]
			miR-106b-25	[66][67]
			miR-106a, miR-93	[67][92]
RYR2	Atrial fibrillation	↑ expression	miR-129*	[68]
			miR-1*, miR133*	[69][70]
			miR-24*	[71][72]
			miR-25	[73][74]
			miR-328	[75][76]
			miR-29c	[77]
SERCA2A	Atrial fibrillation	↓ expression	miR-21*, miR-208b*,	[78][62]
			miR-214*, miR-1954*,	[80][81]
			miR-376b, miR-1*,	[82]
			miR-26a*, miR-30d*,	[82]
			miR-181c*	[82]
			miR-330-5p*	[93]
PLN	Cardiac arrhythmias	-	miR-1, miR-21	[71]
			miR-208a*	[72]
NCX1	Cardiac arrhythmias	-	miR-132	[85]
			miR-1	[80]

* indirect regulation.

2.2. ncRNAs in the Upstroke Phase (If Current)

The hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are the structural pore-forming subunits governing this current, with four HCN isoforms known (HCN1-4), among which HCN4 is the most highly expressed in the sinoatrial and atrioventricular nodes (**Figure 1**A).

D'Souza et al. [35] reported a direct biochemical interaction between miR-423-5p and HCN4 and they further demonstrated that miR-423-5p contributes to training-induced bradycardia by targeting HCN4. Thus miR-423-5p modulates the If current and the heart rate in mice. Yanni et al. [36] reported direct interaction between miR-370-3p and HCN4 (**Figure 1**B).

Indirect evidence on the role of miR-1 and miR-133 regulating HCN isoforms have been also reported. Inversed expression patterns of HCN2 and HCN4 (upregulated) and miR-1 and miR-133 (downregulated) have been reported in age-associated atrial fibrillation [38] myocardial infarction (MI) [39][40], and exercise training [41], yet it remains to be established if these microRNAs can direct target HCN isoforms (**Figure 1**B).

Similarly, no evidence has been reported to date on the direct functional role of microRNAs regulating HCN4 in arrhythmogenic syndromes, supporting the notion that additional studies are required in this context. A summary of the microRNA interaction with the HCN channels is provided on **Table 1**, while their links to distinct cardiac diseases is provided on **Table 2**.

2.3. ncRNAs in Sodium Channel Interacting Proteins

Calmodulin has been extensively reported to directly interact with NaV1.5 (SCN5A) sodium channel and thus to modulate its function [94][95][96][97][98][99][100][101]. Although distinct microRNAs such as miR-1 [102], let-7a [103], miR-625-5p [104], miR-525-5p [105], miR-338-5p [106], miR-185 [107], miR-145 [108], miR-30b-5p [109], and miR-675 [110] have been reported to modulate calmodulin expression, these reports exclusively describe their functional role in cardiac hypertrophy and failed to provide a direct link to sodium channel regulation. To date, the only report linking microRNAs, i.e., miR-26a, and cardiac arrhythmias, i.e., atrial fibrillation, is reported by Qi et al. [111]. Thus, the plausible contribution to sodium channel function by calmodulin interactive protein remains elusive.

3. Role of ncRNAs in Cardiac Repolarization

3.1. ncRNAs in the Early Repolarization (ITO Transient Outward K+ Current)

After cardiac depolarization, the early repolarization process is governed by cardiac transient outward potassium current (ITO). ITO is rapidly activated after a fast increase of the membrane potential, where a short-lived, hyperpolarizing outward K+ current (ITO) makes K+ ions from inside the cells to flow to the extracellular space, causing the transmembrane voltage to decrease. ITO is then quickly deactivated, stopping the repolarization and ending the first phase of the action potential [112].

Several microRNAs have been described to be involved in the regulation of these channels. In particular, in 2007, Zhao and co-workers [42], demonstrated that Kcnd2 is positively regulated by miR-1, through Irx5 inhibition in mice, thus altering the endocardial to epicardial transmural gradient controlled by Kcnd2 within the ventricular cardiomyocytes and thus resulting in ventricular repolarization abnormalities. Kcnd2 is also regulated by miR-223-3p, a microRNA that is remarkably upregulated in a rat model of acute MI and consequently, Kv4.2 protein levels and ITO density were significantly decreased [43] (**Figure 1**B). Such impaired modulation of Kv4.2 protein expression and thus of ITO current can cause prolongation of the action potential duration and thus promote arrhythmias.

3.2. ncRNAs in the Plateau Phase and Terminal Repolarization (IKr, IKs, IKur K+ Current)

Rapid repolarization is followed by a plateau phase, a phase that is characterized by almost equal flow of outward K^+ currents, i.e., through delayed rectifier K^+ channels (IKr, IKs, IKur) and inward Ca^{2+} current regulated by L-type Ca^{2+} channels (ICaL).

3.3. ncRNAs Modulating the Ultra-Rapid Delayed Rectifier K+ Current (IKur)

IKur currents have been recently identified to be modulated by Kv1.5 alpha pore forming subunits, encoded by KCNA5. IKur currents are a major contributor to atrial repolarization [113][114]. Biochemical interaction between miR-1 and human KCNA5 3′UTR has been recently validated [46] yet in vivo functional consequences of miR-1/KCNA5 interactions has only been demonstrated in rat pulmonary hypertension [46] (**Figure 1**B). Therefore, it remains unclear the contribution ncRNAs regulating IKur in the context cardiac electrophysiology.

3.4. ncRNAs Modulating the Rapid Delayed Rectifier K+ Current (IKr)

IKr currents are governed by hERG channels, also known as Kv11.1 [115]. As an homolog of the Drosophila “ether-a-go-go” (EAG) potassium channel, hERG was first cloned in the brain [116]. hERG channels are encoded by KCNH2 and mutations in KCNH2 have been associated to long QT syndrome (type 2; LQTS2) [87]. Ancillary MiRP1 (or KCNE2) subunits, that constitute single transmembrane protein homologous to KCNE1, was shown to associate with HERG channels and modulate IKr biophysical properties [117]. Mutations in KCNE2 have also been associated to long QT syndrome (type 6; LQTS6) [117].

3.5. ncRNAs Modulating the Slow Delayed Rectifier K + Current (IKs)

To date, scarce evidence is available regarding the functional impact of ncRNAs in IKs current modulation. Li et al. [48] examine miR-1/miR-133 levels, the potassium channel KCNE1 and KCNQ1 levels and IKs current in cardiac progenitor cells (CPCs) of normal human hearts. These authors observed that human CPCs expressed KCNE1 and KCNQ1 and possessed functional IKs currents (**Figure 1**B).

3.6. ncRNAs in the Resting Membrane Potential (IK1 Current and Na,K ATPase)

Several microRNAs have been reported to modulate IK1 current in distinct biological contexts. miR-1 levels are increased in patients with coronary artery diseases (CAD) and also in an experimental rat model of MI. In this context, miR-1 silences KCNJ2 protein expression, and also GJA1, by directly targeting their 3´UTRs, respectively [51] (**Figure 1**B). On the contrary hand, miR-1 levels are greatly reduced in human AF as well as in AF experimental models, contributing to upregulation of Kir2.1 subunit, leading thus to increased IK1, being this upregulation of inward-rectifier currents important for AF maintenance [50][52]. Additionally, miR-16 overexpression suppress KCNJ2/Kir2.1 expression in a rat experimental model of MI [53].

A summary of the microRNA interaction with the potassium channels is provided on **Table 1**, while their links to distinct cardiac diseases is provided on **Table 2**.

4. Role of ncRNAs in Conduction Contraction Coupling

4.1. ncRNAs in Calcium Currents (ICa,L Current)

Transgenic mice overexpressing miR-1 resulted in severe electrophysiological defects, causing atrioventricular block [118]. Molecular analysis demonstrates that several key components contributing to the electrical wiring of the heart were altered, such as Cx43 and Kir2.1. Electrophysiological studies revealed that ICa and IK1 currents were decreased. Knockdown of miR-1 overexpression using LNA-anti-miR-1 administration reversed such electrophysiological alteration, demonstrating a pivotal role for miR-1 in cardiac electrophysiology and particularly in calcium homeostasis. More recently, Zhang et al. (2019) demonstrated that transgenic mice overexpressing miR-1976 directly targeted two key calcium channels (i.e., Cav1.2 and Cav1.3, encoded by CACNA1C and CACNA1D, respectively) resulting in SAN dysfunction and thus lower heart rates, a phenotype reminiscent of sick sinus node syndrome in humans [119].

4.2. The Role of ncRNAs in Calcium-Induced Calcium Release

Calcium induced calcium release (CICR) represents the mechanism by which cardiomyocytes can couple conduction and contraction. Ca^{2+} enter the cells through the L-type calcium channels as previously detailed, increasing intracellular Ca^{2+} that leads to massive delivery of Ca^{2+} from the sarcoplasmic reticulum (SR) by the ryanodine receptor (Ryr2). Ca^{2+} is then coupled to troponin, promoting contraction, and is subsequently released from the thin filaments, and re-stored into the SR by calcium ATPase SERCA2 while part of it is also exported outside the cells by the Na^{+}-Ca^{2+} exchanger (NCX1). Importantly, phospholamban (Pln) regulated SERCA2 activity (**Figure 1**A).

Multiple evidences have demonstrated the contribution of microRNAs to Ryr2 function by directly affecting Ryr2 expression such as miR-106b-25 [66][67]. In particular, miR-106b-25 deficient mice displayed increased total Ryr2 protein expression in the atrial tissue, within normal subcellular distribution but Ca^{2+}-spark frequency and total SR- Ca^{2+} leakage were increased [67]. Furthermore, miR106-25 null mice displayed atrial ectopy and were more susceptible to pace-induced AF [67]. Such effects are in part mediated by direct Ryr2 targeting by miR-106a, miR-106b, and miR-93 in mice [67].

5. Conclusions and Perspectives

The relevance of ion channels in governing normal heart rhythm is reflected by the increased incidence of arrhythmias if these ion channels are mutated and/or deregulated [15]. In this scenario, ncRNAs are essential in the maintenance of cardiac function. We have provided herein a state-of-the-art review of the current mechanisms regulated by non-coding RNAs that modulate Na^+, K^+, and Ca^{2+} channel expression and/or function in the cardiovascular system. Ample evidence is available on the direct functional role of microRNAs regulating all phases of the cardiac action potential, such as for example the pore-forming subunit SCN5A expression, through biochemical interaction with its 3´UTR. Importantly, mutations in the 3´UTR can alter such biochemical interactions, and thus impaired normal gene regulation, as recently demonstrated on SCN5A. Furthermore, direct biochemical evidence are also available for those K^+ and Ca^2 channels involved in the repolarization and resting membrane potential phases of the cardiac action potential, with the exception of the IKur current. Surprisingly, our current understanding is still very limited compared to the distinct bioinformatically predicted interactive regulatory networks (**Figure 2**) exemplified herein for pore forming Na+ channels but applicable to all ion channels involved in the cardiac action potential configuration. Furthermore, such plausible interactive networks revealed an intricate number of microRNAs that can simultaneously target distinct components of the repolarization phase, supporting a plausible mechanism underlying co-regulation of the distinct phases of the cardiac action potential. Therefore, increasing efforts should be made to faithfully understand the functional role of microRNAs in cardiac electrophysiology and function, since such knowledge will empower us to better understand the etiology of distinct cardiac electrophysiological defects.

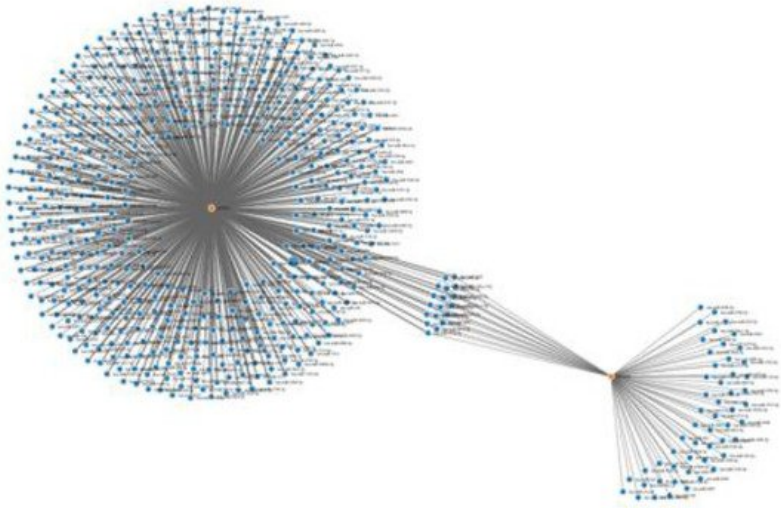

Figure 2. Plausible interactive networks of microRNA regulation on SCN5A and SCN10A as predicted using MirWalk algorithm.

On the other hand, our current understanding of the functional role of lncRNAs in cardiac action potential, and in cardiac electrophysiology at large is still incipient. Only reports on the role of MALAT1 regulating cardiac ITO current throughout the miR-200c/HMGB1 pathway [45], on LncRNA-LINC00472 acting as a miR-24 sponge and thus regulating RYR2 expression [72] and of CircITCH as a natural sponge of miR-330-5p, thereby upregulating SERCA2 [93] have been reported. Therefore, it is expected that additional evidence on the regulatory mechanisms driven by lncRNAs in cardiac electrophysiology will progressively increase in the near future.

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