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Review

Non-Coding RNAs in the Cardiac Action Potential and Their Impact on Arrhythmogenic Cardiac Diseases

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Abstract: 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. Over the last decade, our current understanding of the functional roles of non-coding RNAs have progressively increased. 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. In this review, we provide a comprehensive analysis of the functional contribution of non-coding RNAs, primarily microRNAs, to the normal configuration of the cardiac action potential, as well as their association to distinct types of arrhythmogenic cardiac diseases.

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

Citation: Lozano-Velasco, E.; Aranega, A.; Franco, D. Non-Coding RNAs in the Cardiac Action Potential and Their Impact on Arrhythmogenic Cardiac Diseases. *Hearts* **2021**, *2*, 307–330. https://doi.org/10.3390/hearts2030026

Academic Editors: Francesco Onorati and Matthias Thielmann

Received: 28 February 2021
Accepted: 25 June 2021
Published: 30 June 2021

1. The Electrical Components of the Adult Heart

The adult heart is a four-chambered organ that propels oxygenated blood to the entire body. It is composed of atrial and ventricular chambers, each of them with distinct left and right components, that are connected between them through the atrioventricular valves [1]. Oxygenated blood enters the heart through the pulmonary veins into the left atrium, passes through the atrioventricular mitral valve to the left ventricle and then is expelled to the aorta. Systemic blood is collected into the right atrium through the caval veins, enters the right ventricle along the atrioventricular tricuspid valve, and is subsequently expelled throughout the pulmonary artery into the lungs, before re-entering the heart through the pulmonary veins completing thus a new circulatory cycle [1].

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 [2]. 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 [2].

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 (I_{TO} currents) and three (I_K currents) of the cardiac action potential to finally reach the fourth phase of resting

membrane potential (I_{K1} currents) [3–5]. During the plateau phase, calcium contraction coupling also takes place, by the activation of the $I_{Ca,L}$ currents followed by mobilization of intracellular calcium from the sarcoplasmic reticulum, throughout the calcium-induced calcium release mechanism [6–8]. 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 [4,5]. 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 ($I_{TO;}$ I_{Kur}), plateau ($I_{Kr;}$ I_{Ks}), and final ($I_{Ks;}$ I_{K1}) 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 [9–15].

2. Non-Coding RNAs, Classification, and Function

For a long time, it has been considered that most non-coding RNAs (ncRNAs) were indeed non-functional parts of the genome, and therefore attention was focused on coding RNAs. However, human genome sequencing and ENCODE projects identified that more than 80% of the genome is transcribed into RNA. Surprisingly, only 3% corresponds to coding RNAs, pointing out to an important biological role for ncRNAs [16,17]. In this context, emerging evidences is progressively reporting the essential roles of ncRNAs in distinct biological settings, including herein cell differentiation, homeostasis, and disease (for recent reviews see [18–21]).

NcRNAs are classified in two different categories according to their nucleotide length. Small non coding RNAs are smaller than 200 nucleotides and include microRNAs, small nucleolar RNAs (snoRNAs), piwi-RNAs (piRNAs) as well as transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) [22]. On the other land, long non coding RNAs (lncRNAs) are longer than 200 nucleotides and include therein distinct subtypes such as intronic, enhancer, circular, or intergenic lncRNAs [23,24].

MicroRNAs represent the most studied type of small ncRNAs, besides tRNAs and rRNAs. MicroRNAs are 20–22 ribonucleotides in length and they can bind to 3′ untranslated region of coding RNAs by base-pair complementary, promoting degradation and/or translational blockage [25–27]. Importantly, microRNAs exert key functional roles in multiple biological settings, such as cell differentiation, growth, and homeostasis [28,29].

LncRNAs, on the other hand, are structurally similar to mRNAs but importantly they do not code proteins [30]. LncRNAs can exert transcriptional and post-transcriptional roles, depending on their subcellular localization, i.e., nuclear vs. cytoplasmic. Within the nucleus, they can act as modulators of nuclear gene expression by regulating the epigenetic landscape, scaffolding transcriptional complex or as decoy molecules, whereas in the cytoplasm they can contribute to microRNA degradation, mRNA stability, and/or protein translation see reviews [31–34].

In this review, we aim to provide a state-of-the-art account of the functional contribution of non-coding RNAs to the configuration of the cardiac action potential as well as their consequences if impaired, leading to arrhythmogenic cardiac diseases.

3. Role of ncRNAs in the Cardiac Action Potential

3.1. ncRNAs in the Upstroke Phase (I_{Na} 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 I_{Na} current ($Na_V1.5$) with a smaller contribution of $Na_v1.8$. Importantly, the function of the pore-forming $Na_v1.5$ channel is also modulated by ancillary subunits such as $Na_v\beta1$-$Na_v\beta4$ (Figure 1A). *SCN5A* encodes the voltage-gated Na+ channel $Na_V1.5$. Mutations in *SCN5A* are associated to inherited arrhythmias and cardiomyopathy [35–38]. Moreover, single-nucleotide polymorphisms (SNPs) linked to *SCN5A* splicing, localization, and function are also associated to sudden cardiac death [39,40]. *SCN10A* encodes the voltage-gated Na+ channel NaV1.8. Importantly, mutations in *SCN10A* have also been linked to sudden unexplained death [41], atrial fibrillation [42,43], and Brugada syndrome [40,44,45]. Furthermore, *SCN5A* and *SCN10A* share common regulatory elements that are relevant for cardiac function [46].

Distinct sets of evidence have been provided on the functional roles of microRNAs modulating *SNC5A* expression. Daimi et al. [47] firstly reported that miR-98, miR-106, miR-200, and miR-219 directly regulated human *SCN5A* while miR-125 and miR-153 regulate it indirectly. Functional analysis in HL1 cardiomyocytes revealed that miR-219 and miR-200 have independent and opposite effects on *Scn5a* expression and thus subsequently on I_{Na} sodium current, provoking impaired rhythm contraction of the cardiomyocytes. Importantly, in vivo miR-219 administration abolishes QRS prolongation after flecainide intoxication in mice without altering normal cardiac rhythm (Figure 1B). In addition, Zhao et al. [48] reported that miR-192-5p directly targets human SCN5A, affecting therein the peak I_{Na} current density. Furthermore, these authors demonstrated upregulation of miR-192-5p in left atrial biopsies of atrial fibrillation (AF) patients as compared to controls, while *SCN5A*/$Na_V1.5$ was downregulated. Curiously, miR-1, a highly expressed microRNA in cardiac development and arrhythmogenic cardiac diseases does not modulate SCN5A expression (Figure 1B) [49]. Additional evidences described by Poon et al. [50] demonstrated that miR-200c can modulate *SCN5A* expression in human embryonic stem cells (ESC)-derived cardiomyocytes, yet direct biochemical evidences are lacking. In sum, our current understanding of the functional role of microRNAs regulation SCN5A expression is still scarce.

A more indirect dataset has also been reported to influence SCN5A expression in distinct arrhythmogenic contexts. For example, Li et al. [51] identified miR-143 as an upstream regulator of EGR1, which can modulate *SCN5A*/NaV1.5 expression (Figure 1B). Zhang et al. [52] recently identified a synonymous SNP (rs1805126) close to a miR-24 site within the *SCN5A* coding sequence. They also reported that miR-24 potently suppresses SCN5A expression and I_{Na} current and that rs1805126 minor allele highly associates with decreased SCN5A expression in heart failure patients (Figure 1B). Surprisingly, homozygous heart failure patients for rs1805126 minor allele displayed reduced ejection fraction and increased mortality while ventricular tachyarrhythmias were not increased. In the same line of thinking, Daimi et al. [53] screened for plausible genetic alterations in SCN5A as well as five additional candidate genes (GPD1L, SCN1B, KCNE3, SCN4B, and MOG1) associated to Brugada syndrome, within the coding sequence, the flanking intronic and the 5′ and 3′UTR regions. Genetic variants such as hsa-miR-219a-rs107822 and a novel SNP that created an additional miR-1270 binding site (Figure 1B) were identified within the SCN5A 3′UTR, but no relevant coding sequence variants. Thus, most SCN5A variants were localized in non-coding regions. Furthermore, the lack of genotype-phenotype correlations supported the complexity of the genetic bases of Brugada syndrome and it suggests that combination of multiple genetic factors, rather than a single variant is behind the onset of this syndrome.

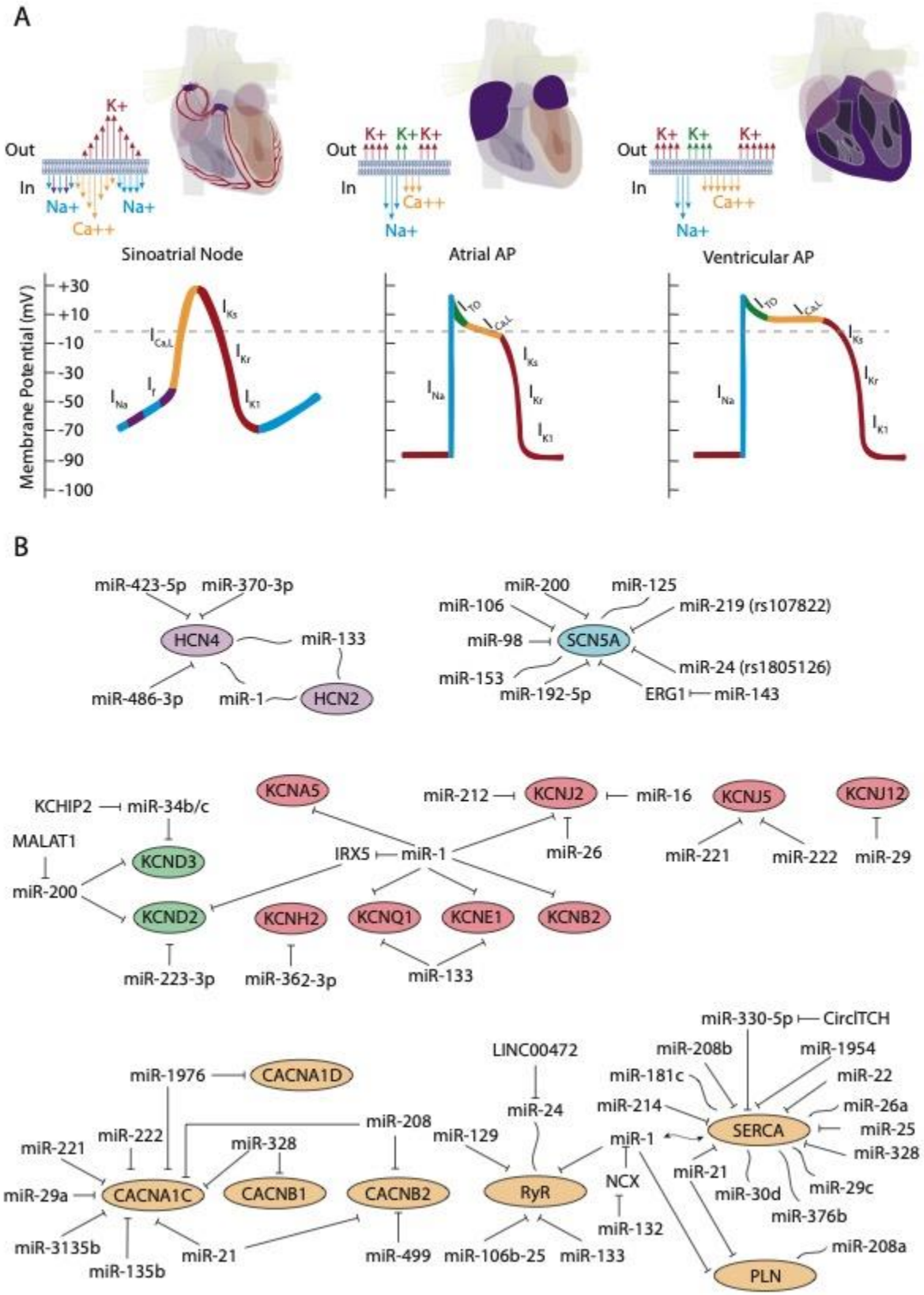

Figure 1. (**A**) Graphical representation of the cardiac action potential in the sinoatrial node (and also the atrioventricular node) and in contractile working myocardium of the atrial and ventricular chambers. (**B**) Schematic representation of the functional roles ncRNAs within the cardiac action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

While emerging evidence is progressively increasing on the functional role of microRNAs on the regulation of SCN5A/$Na_V1.5$, to date no information is available upon their putative contribution to sodium channel ancillary subunits in the cardiovascular contexts, although some reports for miR-449a, miR-34a, miR-133b, miR-143-3p, and miR-1-3p modulating SCN2B/$Na_V\beta2$ [54–57], miR-375 modulating SCN3B/$Na_V\beta3$ [58], and miR-3175 and miR-424-5p modulating SCN4B/$Na_V\beta4$ [59,60] have been described in other biological contexts.

Similarly, the impact of microRNAs in the slow component of the I_{Na} 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 [61,62]. 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
I_{Na}	miR-98, miR-106, miR-200, miR-219, miR-125, miR-153	SCN5A	INa ↑/INa ↓	[47,53]
	miR-192-5p		INa ↓	[48]
	miR-200c		-	[50]
	miR-143		INa ↓	[51]
	miR-24		INa ↓	[52]
If	miR-423-5p	HCN4	If ↓	[63]
	miR-370-3p		If ↓	[64]
	miR-486-3p		If ↓	[65]
	miR-1, miR-133		If ↑	[66–69]
	miR-1, miR-133	HCN2	If ↑	[66–69]
I_{TO}	miR-1	KCND2	ITO ↓	[70]
	miR-223-3p		ITO ↓	[71]
	miR-34b/c		ITO =	[72]
	miR-200		ITO ↓	[73]
	miR-200	KCND3	I_{TO} ↓	[73]
I_{Kur}	miR-1	KCNA5	I_{Kur} ?	[74]
I_{Kr}	miR-134, miR-103a-1, miR-143, miR-3619	hERG	I_{Kr} ↓	[75]
I_{KS}	miR-1, miR-133	KCNE1	I_{KS} ↓	[76,77]
	miR-1, miR-133	KCNQ1	I_{KS} ↓	[76]
	miR-1, miR-133	KCNB2	I_{KS} ↓	[77]
I_{K1}	miR-1	KCNJ2	IK1 ↓/IK1 ↑	[49,78,79]
	miR-16		IK1 ↓	[80]
	miR-26		IK1 ↑	[81,82]
	miR-212		IK1 ↓	[83,84]
	miR-29	KCNJ12	I_{K1} ↓	[85]
	miR-221/222	KCNJ5	I_{K1} ↓	[86]

Table 1. *Cont.*

Current	microRNA	Gene	Function	Reference
$I_{Ca,L}$	miR-328	CACNA1C	$I_{Ca,L}$ ↓	[87]
	miR-21, miR-208b		ICa,L ↓	[88,89]
	miR-20a, miR-3135b		ICa,L ↓	[90]
	miR-499		ICa,L ↓	[91]
	miR-135b		ICa,L ↓	[92]
	miR-221/222		ICa,L ↓	[86]
	miR-328	CACNB1	ICa,L ↓	[87]
	miR-21, miR-208b	CACNB2	ICa,L ↓	[88,89]
	miR-499		ICa,L ↓	[91]
	miR-329		ICa,L ↓	[91]
CICR	miR-106b	RYR2	-	[93,94]
	miR-129			[95]
	miR-1, miR-133			[96,97]
	miR-23			[98,99]
	miR-25	SERCA2A	-	[100,101]
	miR-328			[102,103]
	miR-29c			[104]
	miR-21			[105]
	miR-208b			[89]
	miR-22			[106]
	miR-214			[107]
	miR-1954			[108]
	miR-376b, miR-1, miR-26a, miR-30d, miR-181			[109]
	miR-1, miR-21	PLN	-	[110]
	miR-208a			[111]
	miR-132	NCX1	-	[112]
	miR-1			[107]

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	-	[35–38]
	Sudden death	SNPs	-	[39,40]
	Brugada syndrome	SNPs/↓ expression	miR-219	[47,53]
	Atrial fibrillation	↓ expression	miR-192-5p	[48]
	Heart failure	SNPs/↓ expression	miR-24	[52]
SCN10A	Sudden death	Mutation	-	[41]
	Atrial fibrillation		-	[42,43]
	Brugada syndrome		-	[29,44,45]

Table 2. *Cont.*

Gene	Disease	Alteration	Mir Related	Reference
HCN4	Bradycardia	↓ expression	miR-423-5p, miR-370-3p	[63,64]
	Age atrial fibrillation	↑ expression	miR-1, miR-133	[66]
	Myocarial infarction	↑ expression	miR-1, miR-133	[67,68]
HCN2	Age atrial fibrillation	↑ expression	miR-1, miR-133	[66]
	Myocardial infarction	↑ expression	miR-1, miR-133	[67,68]
KCND2	Sudden death	↓ expression	miR-1	[70]
	Acute myocardial infarction	↓ expression	miR-223-3p	[71]
	Myocardial infarction	↓ expression	miR-200c	[73]
KCNH2	LQT syndrome (type 2)	Mutation	-	[113]
	Heart failure	↓ expression	miR362-3p	[114]
KCNE2				
LQT syndrome (type 6)				
LQT syndrome (type 1)	LQT syndrome (type 1)	↓ expression	-	[115–117]
	Atrial fibrillation	↓ expression	miR-1	[77]
KCNB2				
Atrial fibrillation	Myocardial infarction	↓/↑ expression	miR-1, miR-16	[78,81]
	Atrial fibrillation	↑ expression	miR-1, miR-26	[49,79,82]
	Heart failure	↓ expression	miR-212	[84]
KCNJ12	Myocardial infarction	↓ expression	miR-29	[85]
KCNJ5	Atrial fibrillation	↓ expression	miR-221/222	[86]
CACNA1C	Atrial fibrillation	↓ expression	miR-221/222	[86]
			miR-328	[87]
			miR-21	[88]
			miR-208b	[89]
			miR-29b, miR-3135b	[90]
CACNB2	Atrial fibrillation	↓ expression	miR-21	[88]
			miR-208b	[89]
			miR-499, miR-329	[91]
RYR2	Atrial fibrillation	↑ expression	miR-106b-25	[93,94]
			miR-106a, miR-93	[94,118]
			miR-129*	[95]
			miR-1*, miR133*	[96,97]
			miR-24*	[98,99]

Table 2. *Cont.*

Gene	Disease	Alteration	Mir Related	Reference
SERCA2A	Atrial fibrillation	↓ expression	miR-25	[100,101]
			miR-328	[102,103]
			miR-29c	[104]
			miR-21*, miR-208b*,	[89,105]
			miR-214*, miR-1954*,	[107,108]
			miR-376b, miR-1*,	[109]
			miR-26a*, miR-30d*,	[109]
			miR-181c*	[109]
			miR-330-5p*	[119]
PLN	Cardiac arrhythmias	-	miR-1, miR-21	[98]
			miR-208a*	[99]
NCX1	Cardiac arrhythmias	-	miR-132	[112]
			miR-1	[107]

* indirect regulation.

3.2. ncRNAs in the Upstroke Phase (If Current)

The upstroke phase of the cardiac action potential in slow conducting cells, i.e., sinoatrial and atrioventricular nodal myocytes, is primarily modulated by the funny current, i.e., I_f current. Almost 40 years ago, the 'funny' (pacemaker, I_f) current was firstly described in sinoatrial node (SAN) myocytes [120]. 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 1A).

Current information regarding the functional role of ncRNAs, particularly microRNAs, is progressively emerging. D'Souza et al. [63] 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 I_f current and the heart rate in mice. Yanni et al. [64] reported direct interaction between miR-370-3p and HCN4 (Figure 1B). Gain-of-function experiments in vitro demonstrate its role provoking bradycardia and loss-of-function assays in vivo revealed that silencing miR-370-3p in a heart failure mouse model, increases HCN4 mRNA and protein expression, increasing therefore I_f current in the sinus node and thus blunting sinus bradycardia. More recently, a microRNA array analysis in the human sinoatrial node vs. surrounding atrial tissue identified 18 upregulated and 48 downregulated microRNAs [65]. Among them, the authors demonstrate that miR-486-3p was directly targeting HCN4 and, if over-expressed in rat sinoatrial node preparations, cardiomyocyte beating was reduced by almost a third (Figure 1B). Thus, these data demonstrate that several microRNAs can influence HCN4 expression and thus I_f current, impacting therefore in heart rate control.

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 [66] myocardial infarction (MI) [67,68], and exercise training [69], yet it remains to be established if these microRNAs can direct target HCN isoforms (Figure 1B).

No information is currently available about the plausible regulatory effects of microRNAs in HCN1 and HCN3 in the cardiovascular system, although in other biological

contexts, such as in the brain, it has been identified that miR-706 targets HCN1 [121]. 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.

3.3. ncRNAs in Sodium Channel Interacting Proteins

It has been recently reported that $Na_V1.5$ may be part of multi-protein complexes composed of $Na_V1.5$-interacting proteins which regulate channel expression and function [122,123]. These $Na_V1.5$ interacting proteins can be classified as anchoring/adaptor proteins, enzymes interacting with and modifying the channel, and proteins that modulate $Na_V1.5$ biophysical upon binding. Importantly, mutations in several of genes encoding these regulatory proteins have also formed in patients with cardiac arrhythmias [124–127]. To date, at least 17 different interacting proteins have been described [123], among which only a small subset of them have been reported to be modulated by microRNAs—i.e., calmodulin, caveolin, and Nedd4 ubiquitin ligases—as detailed below.

Calmodulin has been extensively reported to directly interact with $Na_V1.5$ (*SCN5A*) sodium channel and thus to modulate its function [128–135]. Although distinct microRNAs such as miR-1 [136], let-7a [137], miR-625-5p [138], miR-525-5p [139], miR-338-5p [140], miR-185 [141], miR-145 [142], miR-30b-5p [143], and miR-675 [144] 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. [145]. Thus, the plausible contribution to sodium channel function by calmodulin interactive protein remains elusive.

Caveolin has been recently linked to $Na_V1.5$ function [146,147]. To date, only miR-22 have been reported to target caveolin-3 in the cardiovascular setting. Similarly, as for microRNAs-calmodulin interactions, the implications for sodium channel function or for cardiac electrophysiology at large have not been reported [148,149].

Nedd4 ubiquitin ligases role in $Na_v1.5$ have also been reported [150–152]. miR-1 targets Nedd4 in *Drosophila* and Nedd4l in mammals, supporting a plausible role modulated trafficking or degrading Need4/Need4l substrates in the heart—such as Scn5a [153]—yet direct evidence remains to be elucidated.

4. Role of ncRNAs in Cardiac Repolarization

Cardiac repolarization can be divided into different phases, starting with a rapid repolarization phase, followed by a plateau phase and ending with the terminal phase by which the resting membrane potential is reestablished. The rapid repolarization is mainly controlled by the rapidly activating transient outward (I_{TO}). The plateau phase contains the contribution of the rapid (I_{Kr}) and slow (I_{Ks}) delayed rectifier K+ currents, as well as the ultra-rapid delayed rectifier (I_{Kur}) currents, which are counterbalanced by the depolarization contribution of L-type calcium current (I_{Ca}). Finally, I_{Kr} and the inward rectifier K+ current (I_{K1}) contribute with repolarizing currents at the terminal phase of the action potential, reestablishing the resting membrane potential [154] (Figure 1A).

4.1. ncRNAs in the Early Repolarization (I_{TO} Transient Outward K+ Current)

After cardiac depolarization, the early repolarization process is governed by cardiac transient outward potassium current (I_{TO}). I_{TO} is rapidly activated after a fast increase of the membrane potential, where a short-lived, hyperpolarizing outward K+ current (I_{TO}) makes K+ ions from inside the cells to flow to the extracellular space, causing the transmembrane voltage to decrease. I_{TO} is then quickly deactivated, stopping the repolarization and ending the first phase of the action potential [155]. I_{TO} has two components, i.e., fast (I_{TOf}) and slow (I_{TOf}) components. I_{TOf} is the principal subtype present in human atria while both

I_{TOf} and I_{TOs} are present in the ventricles [156]. The channel leading to I_{TOf} current is formed by assembly of K_v4.2 (*KCND2*) or K_v4.3 (*KCND3*) subunits or a combination of both, while I_{TOs} current channel is formed by K_v1.4 (KCNA4) subunits [155].

Several microRNAs have been described to be involved in the regulation of these channels. In particular, in 2007, Zhao and co-workers [70], 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, K_v4.2 protein levels and I_{TO} density were significantly decreased [71] (Figure 1B). Such impaired modulation of K_v4.2 protein expression and thus of I_{TO} current can cause prolongation of the action potential duration and thus promote arrhythmias.

Several evidences have demonstrated that KChip2 associates with and modulates the Kv4 family of potassium channels [157,158]. Importantly, KChip2 protein negatively modulates miR-34b/c expression that in turn targets Kv4.3, modulating I_{TO} current. Importantly Kv4.2 and Kv1.4 are not regulated by miR-34, thus modulation of I_{TO} current is only observed on this fast ($I_{TO,f}$), but not on the slow ($I_{TO,s}$) component. Beside regulating $I_{TO,f}$, miR-34 it also modulates *Scn5a* and *Scn1b* expression and thus I_{Na} current [150]. Thus these data identified KChip2/miR-34 axis as a core regulator of electrical dysfunction, suggesting miR-34 as a therapeutic target for treating arrhythmogenesis in heart disease [72] (Figure 1B).

In addition to the functional role of microRNAs modulating I_{TO} current, it has been recently elucidated the possible relation between lncRNAs and I_{TO} currents. In particular, MALAT1 mediates cardiac I_{TO} current regulating miR-200c/HMGB1 pathway that controls KCND2 and KCND3 expression [73] in a rat experimental model of MI (Figure 1B). Furthermore, MALAT1 knockdown improved several cardiac electrophysiological parameters, particularly I_{TO} current, in post-MI cardiomyocytes and thus provides evidence that it might represent a novel potential therapeutic target for MI.

4.2. ncRNAs in the Plateau Phase and Terminal Repolarization (I_{Kr}, I_{Ks}, I_{Kur} 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 (I_{Kr}, I_{Ks}, I_{Kur}) and inward Ca^{2+} current regulated by L-type Ca^{2+} channels (I_{CaL}).

4.3. ncRNAs Modulating the Ultra-Rapid Delayed Rectifier K+ Current (I_{Kur})

I_{Kur} currents have been recently identified to be modulated by K_v1.5 alpha pore forming subunits, encoded by KCNA5. I_{Kur} currents are a major contributor to atrial repolarization [159,160]. Biochemical interaction between miR-1 and human KCNA5 3′UTR has been recently validated [74] yet in vivo functional consequences of miR-1/KCNA5 interactions has only been demonstrated in rat pulmonary hypertension [74] (Figure 1B). Therefore, it remains unclear the contribution ncRNAs regulating I_{Kur} in the context cardiac electrophysiology.

4.4. ncRNAs Modulating the Rapid Delayed Rectifier K+ Current (I_{Kr})

I_{Kr} currents are governed by hERG channels, also known as K_v11.1 [161]. As an homolog of the *Drosophila* "ether-a-go-go" (EAG) potassium channel, hERG was first cloned in the brain [162]. hERG channels are encoded by KCNH2 and mutations in KCNH2 have been associated to long QT syndrome (type 2; LQTS2) [113]. Ancillary MiRP1 (or KCNE2) subunits, that constitute single transmembrane protein homologous to KCNE1, was shown to associate with HERG channels and modulate I_{Kr} biophysical properties [163]. Mutations in KCNE2 have also been associated to long QT syndrome (type 6; LQTS6) [163].

Mourad [114] has shown that miR-362-3p was significantly higher in the heart failure with reduced ejection fraction (HFrEF) group compared to controls whereas hERG expression was significantly lower in the HFrEF group compared to controls [114] (Figure 1B).

However, direct biochemical interaction evidence between miR-362-3p and hERG have not been reported. Growing evidence is showing that microRNAs are involved in functional modulation of the hERG/KCNH2 pathway. In particular, miR-134, miR-103a-1, miR-143, and miR-3619 significantly suppressed hERG mRNA expression in U2OS cells [75]. Furthermore, these authors demonstrated that miR-103a-1 decreased the I_{Kr} activation current and I_{Kr} tail current amplitude of hERG channel, and also is accelerated the hERG protein channel inactivation process [75] in HEK293T cells, yet direct evidence in cardiomyocytes remains elusive. Other two microRNAs have been demonstrated to regulate hERG expression in pathological contexts, i.e., cancer. MiR-328 [164] and miR-362-3p [165] reduced hERG-related current and inhibited breast cancer cell proliferation. In summary, scarce information is currently available on the functional role of ncRNAs regulating I_{Kr} current in the cardiovascular setting.

4.5. ncRNAs Modulating the Slow Delayed Rectifier K + Current (I_{Ks})

I_{Ks} channels are slowly activated during the plateau phase by depolarizing voltages. The pore-forming subunit KCNQ1 (KvLQT1 or K_v7.1) was first identified by positional cloning and linked to long QT syndrome (type 1; LQT1) [166]. Importantly, KCNE1, also known as Mink [115], represent the ancillary subunit that when co-assembles with KCNQ1 provides to this channel its unique slow kinetics similar to that of the native I_{Ks} current in cardiomyocytes [116,117]. In addition, KCNB2, that is weakly expressed in the heart [117] as compared to other tissues, have been reported to affect cardiac K+ currents, playing a pivotal role in cell excitability [167].

To date, scarce evidence is available regarding the functional impact of ncRNAs in I_{Ks} current modulation. Li et al. [76] examine miR-1/miR-133 levels, the potassium channel KCNE1 and KCNQ1 levels and I_{Ks} current in cardiac progenitor cells (CPCs) of normal human hearts. These authors observed that human CPCs expressed KCNE1 and KCNQ1 and possessed functional I_{Ks} currents (Figure 1B). Moreover, high-level glucose exposure in human CPCs lead to augmented miR-1 and miR-133 expression and concomitant decreased KCNE1 and KCNQ1 expression, and thus I_{Ks} reduction. These data support a role for miR-1/miR-133 in I_{Ks} regulation (Figure 1B); however, their functional roles in native and mature cardiomyocytes remains undetermined. Although the functional effects of KCNB2 on the cardiovascular system have been scarcely explored, it has been demonstrated that miR-1 modulates KCNB2. In vivo experiments found that the upregulation of miR-1 reduced in KCNE1 and KCNB2 expression, shortened the atrial effective refractory period (AERP) of the right atrium and enhanced the inducibility of AF [77] (Figure 1B).

4.6. ncRNAs in the Resting Membrane Potential (I_{K1} Current and Na,K ATPase)

Terminal repolarization is increased after the plateau phase a process mainly governed by the rapid delayed rectifier current (I_{Kr}) and the inward rectifier K^+ current (I_{K1}) [168,169]. I_{K1} stabilizes the resting membrane potential and is responsible for shaping the initial depolarization and final repolarization of the cardiac action potential. The Kir2 subfamily members, Kir2.1, Kir2.2, Kir2.3, and Kir2.4 contribute to the cardiac I_{K1} current [170] and they are encoded by KCNJ2, KCNJ12, KCNJ4, and KCNJ14, respectively.

Several microRNAs have been reported to modulate I_{K1} 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 [78] (Figure 1B). 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 I_{K1}, being this upregulation of inward-rectifier currents important for AF maintenance [49,79]. Additionally, miR-16 overexpression suppress KCNJ2/Kir2.1 expression in a rat experimental model of MI [80]. Further in vivo experimental analysis also demonstrates that valsartan, an angiotensin II inhibitor, can decrease miR-16, and thus increase KCNJ2/Kir2.1, expression, while angiotensin II administration provoked the opposite effects [80]. miR-26 have

been reported to be downregulated in AF patients. Experimental over-expression studies in mice demonstrated that miR-26 can modulates KCNJ2/Kir2.1 expression. Furthermore, miR-26 endogenous knockdown in mice promoted AF while ectopic expression reduced AF vulnerability, demonstrating an essential role for miR-26 regulating I_{K1} current and thus AF onset [81,82] (Figure 1B). Finally, miR-212, one of the most upregulated miRNAs in human heart failure [83], also targets KCNJ2, severely downregulating I_{K1} current and thus contributing to the risk of cardiac arrhythmia during the process of myocardial remodeling en route to heart failure [84] (Figure 1B). In addition to the regulation of KCNJ2 by microRNAs, KCNJ12 has been reported to be regulated by miR-29 [85] as well as KCNIP2 (Figure 1B). miR-29 expression levels are significantly increased in the ischemic region of MI mouse hearts and both KCNJ12 and KCNIP2 protein/mRNA expression levels were significantly decreased [85]. Thus, modulation of miR-29 expression is highly relevant given its role controlling the cardiac membrane resting potential, thought I_{K1} current regulation, and thus represents a plausible therapeutic target against ischemic arrhythmias. Recently, it has been evidenced that miR-221 and miR-222 target KCNJ5 and, therefore, potentially contribute to disturbed cardiac excitation generation and propagation [86] (Figure 1B). 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.

The resting membrane potential of the cardiac action potential, beside the contribution of IK1 current, is also modulated by the Na,K-ATPase. Na,K-ATPase is composed of four distinct alpha (ATP1A1 to ATP1A4) and beta (ATP1B1 to ATP1B4) subunits and it regulates sodium export and potassium import across the plasma membrane in a large variety of cells. Within the heart, the most prominently expressed Na,K-ATPase alpha subunits are ATP1A1, ATP1A2, and ATP1A3 [171–178] and ATP1B1 and ATP1B2 as Na,K-ATPase beta subunits [171–174,177,179–181]s. Our current understanding of the functional role of ncRNAs in Na,K-ATPase biology is scarce. Drummond et al. [182,183] demonstrate that impairment signaling of Na,K-ATPase leads to upregulation of miR-29b-3p in the heart of a model of chronic kidney disease, a process that is modulated by the upregulation of this microRNA in cardiac fibroblasts. Besides this study, no additional evidence has been reported to date about the contribution of microRNAs and/or lncRNAs regulating Na,K-ATPase expression and/or function in the cardiovascular system.

5. Role of ncRNAs in Conduction Contraction Coupling

5.1. ncRNAs in Calcium Currents ($I_{Ca,L}$ Current)

Ca^{2+} ions play a pivotal role in the excitation and contraction of the heart. Ca^{2+} influx within ventricular myocytes occurs through voltage-activated Ca^{2+} channels, contributing to the plateau phase of the cardiac action potential. L-type Ca^{2+} channels are considered the most important contributors to the Ca^{2+} influx in the working myocardium (Figure 1A). There are four members on the L-type Ca^{2+} channels family, namely $Ca_v1.1$ to $Ca_v1.4$. L-type calcium channels (Ca_v1) represent one of the three major classes (Ca_v1–3) of voltage-gated calcium channels.

Transgenic mice overexpressing miR-1 resulted in severe electrophysiological defects, causing atrioventricular block [184]. 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 I_{Ca} and I_{K1} 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 [185].

In 2010, Lu et al. [87] demonstrated that miR-328 targets L-type Ca^{2+} channel genes—i.e., CACNA1C and CACNB1—contributing to the adverse atrial electric remodeling in AF

(Figure 1B). Using an experimental canine model atrial tachypacing, these authors demonstrated that miR-223, miR-328, and miR-664 were upregulated whereas miR-101, miR-133, miR-145, miR-320, miR-373, and miR-499 were downregulated. miR-328 upregulation was subsequently validated in atrial tissues from AF patients. Forced expression of miR-328 increased the vulnerability of dogs to electrical AF induction while miR-328 transgenic mice developed AF. Electrophysiological analysis demonstrated that I_{Ca} was substantially decreased while I_{TO}, I_{Kur} and I_{K1} currents were unaltered. During chronic human AF, miR-21 and miR-208b expression levels are increased, promoting a decrease of $I_{Ca,L}$ density by downregulating Ca^{2+} channels subunits expression, particularly, CACNA1C and CACNB2 [88,89] (Figure 1B). Therefore miR-21 and miR-328 leads to $I_{Ca,L}$ downregulation and thus to shortening in the cardiac action potential that might be responsible to self-perpetuate AF. In addition, miR-29a and miR-3135b have been shown to be differentially expressed in AF, and both microRNAs directly target CACNA1C [90]. miR-29a overexpression assays in atrial myocytes further demonstrated a significant reduction on $I_{Ca,L}$ current density. However, the functional roles of these microRNAs in vivo remains to be determined. Similarly, increased miR-499 have been reported in permanent AF patients and forced expression of miR-499 induces the downregulation of CACNB2 expression in HL1 atrial cardiomyocytes, resulting also into downregulation of the pore forming alpha subunit CACNA1C protein levels. Furthermore, these authors demonstrated that miR-329 is a direct target of CACNB2 and thus provide circumstantial evidence that miR-329 may contribute to the electrical remodeling in AF [91], yet in vivo experiments are required to fully validate such a hypothesis (Figure 1B).

Moreover, L-type calcium channels play important role in cardiac hypertrophy. Recent studies in mice revealed that miR135b is significantly diminished in cardiac hypertrophy. Interestingly, miR-135b overexpression attenuated cardiac hypertrophy by directly targeting CACNA1C (Figure 1B), reducing I_{Ca} density and shortening the cardiac action potential duration [92]. miR-221/222 expression levels have been analyzed in a mouse model of severe cardiac hypertrophy that also displayed electrophysiological alterations in absence of fibrosis. Both microRNAs were increased in cardiomyocytes but not in cardiac fibroblasts. miR-221 and miR-222 contributed to L-type Ca^{2+} channels regulation by directly targeting CACNA1C leading to reduced I_{Ca} density [86] (Figure 1B). Curiously, miR-221 also directly targeted Kcnj5 while miR-22 targeted Kcnj5, Cacna2b, and Kcnd2, yet the functional consequences on their corresponding ion channels remains to be determined. Recently, Liu et al. [93,186], demonstrated that miR-145 effectively alleviates heart failure related cardiac remodeling by improving cardiac dilation, fibrosis, intracellular Ca^{2+} mishandling and electrophysiological instability in a myocardial infarct mouse model. Particularly, these authors demonstrated that miR-145 is significantly reduced in an experimental rat model of heart failure, and miR-145 overexpression reversed heart failure-induced I_{Ca} density reduction, intracellular Ca^{2+} homeostasis as well as the prolongation of the QTc interval. Whereas evidence on the modulatory role of microRNAs in calcium channel expression is still incipient, these data suggest that targeting discrete microRNAs might represent a novel strategy to attenuate cardiac hypertrophy. A summary of the microRNA interactions with the calcium channels is provided on Table 1, while their links to distinct cardiac diseases is provided on Table 2.

5.2. 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 1A).

Multiple evidences have demonstrated the contribution of microRNAs to Ryr2 function by directly affecting Ryr2 expression such as miR-106b-25 [93,94]. 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 [94]. Furthermore, miR106-25 null mice displayed atrial ectopy and were more susceptible to pace-induced AF [94]. Such effects are in part mediated by direct Ryr2 targeting by miR-106a, miR-106b, and miR-93 in mice [94]. Importantly, only a subset of AF patients displayed impaired miR-106-25 expression, while RYR2 was in all cases increased, supporting the notion that additional players contribute to AF development [118]. Ryr2 regulation by microRNAs has also been reported as indirect mechanisms such as for the case of miR-129 that regulates Grind2 and thus Ca^{2+} signaling [95] or by modulating Ryr2 phosphorylation such as miR-1 /miR-133 [96,97]. It has been demonstrated an enhanced excitation-contraction coupling in miR-133- [96] and miR-1 [97] -overexpressing myocytes, respectively, a process that stems from increased responsiveness of Ryr2 to triggering Ca^{2+}. Importantly, that miR-133 and miR-1 can directly target the catalytic subunits of PP2A phosphatase, and since inhibition of phosphatase activity results in the enhanced propensity of ventricular myocytes toward the generation of Ca^{2+}-dependent afterdepolarizations, these results indicate the involvement of muscle-specific miRNAs in the regulation of CaMKII-dependent phosphorylation of the Ryr2 via PP2A. Additional evidence of indirect modulation of Ryr2 function have been reported by Li et al. [98] by in vivo miR-24 inhibition in mice, resulting in restorage of the Ca^{2+} transient amplitude, and thus the excitation–contraction coupling impairment produced by transverse aortic constriction (TAC)-induced cardiac hypertrophy. However, the precise mechanisms as how miR-24 influences Ryr2 remains elusive. Similarly, LncRNA-LINC00472 modulation also regulates Ryr2 expression, since it acts as a miR-24 sponge, yet the precise mechanisms are unclear [99] (Figure 1B).

Similarly, increasing evidences have been reported on the functional contribution of microRNAs regulating SERCA2A/ATPa2a. miR-25 [100,101], miR-328 [102,103], and miR-29c [104] can directly regulate SERCA2A. By generating miR-25 sponges, it was reported that SERCA2a and PLN expression were increased but not Ncx, Ryr2 or Ip3r2, yet no calcium coupling electrophysiological measurements were provided [100]. Importantly, miR-25 is upregulated in patients with severe heart failure, expressed in cardiomyocytes, and directly targets Serca2a, thus regulating Ca^{2+} kinetics in vitro [101]. Moreover, in vivo miR-25 administration downregulated Serca2a and provokes a progressive decline in fractional shortening in mice while anti-miR-25 in vivo injections in an experimental mouse model of chronic pressure overload, substantially improving cardiac function [101]. SERCA2 has been reported to be direct target of miR-328 [102] and also to increase intracellular Ca^{2+} concentrations in H9c2 cardiomyocytes [103]. In addition, miR-29c have been reported to directly interact with SERCA by dual luciferase assays and thus to provoke protein downregulation and impaired Ca^{2+} reuptake in vitro. Furthermore, in vivo analysis of antimiR-29 administration restores cardiac contractility in a cardiomyopathy mouse model caused by HIF1apha deficiency [104].

On the other hand indirect targeting evidences have been provided for miR-21 [105], miR-208b [89], miR-22 [106], miR-214 [107], miR-1954 [108], miR-376b, miR-1, miR-26a, miR-30d, and miR-181c [109] (Figure 1B). miR-21 overexpression leads to increased calcium transients amplitude, yet no biochemical assays of direct SERCA interactions are reported [105]. miR-208b expression displays inverse correlations with SERCA levels, $I_{Ca,L}$ density and miR-208b overexpression impairs calcium handling in HL1 cardiomyocytes but similarly biochemical interaction evidences are lacking [89]. miR-22 null mutants display reduced Serca2a transporting activity and lower SR Ca^{2+} load. Decreased Serca2a protein and mRNA expression is observed in miR-22 null mutants while Pln, Ncx, Casq2, and Ryr2 displayed no significant differences [106]. However, it remains to be elucidated the precise mechanisms of such impaired Serca2 expression and function. Finally, for miR-214 [107], miR-1954 [108], miR-376b, miR-1, miR-26a, miR-30d, and miR-181c [109] only inverse

correlation of microRNA and Serca2 expression in distinct biological contexts are provided without any additional mechanistic proof.

Curiously, CircITCH acts as a natural sponge of miR-330-5p, thereby upregulating SERCA2 and opening novel ways for SERCA2A post-transcriptional regulation [119]. Additional bioinformatic approaches have investigated microRNA-SERCA2A interactions [187], yet further functional studies are needed for verification. Importantly, SERCA2A impaired expression—e.g., adenovirus mediated overexpression—also leads to microRNA deregulation, such as for miR-1 [188], supporting a fine-tuned cross-talk between ncRNAs and calcium homeostasis.

In contrast to the current evidence of SERCA2A modulation by microRNAs, scarce evidences are reported on phospholamban post-transcriptional regulation. Soller et al. [110] described that miR-1 and miR-21 can target Pln, releasing thus SERCA inhibition and also indirect evidence are available that miR-208a can modulate Pln expression [111] (Figure 1B), yet the precise electrophysiological consequences of such modulation roles in in vivo remains unanswered.

Similarly to Pln, scarce evidences are reported for Ncx1 regulation by microRNAs. Hong et al. [112] described that miR-132 targets Ncx1 and Melo et al. [107] that miR-1 targets Ncx1, yet the electrophysiological consequences of such interactions remains elusive. Additional evidences have been reported in other biological settings, such as for miR-103 targeting Ncx1 in the brain [189], yet they are similarly scarce (Figure 1B). A summary of the microRNA interaction with the genes involved in CICR is provided on Table 1, while their links to distinct cardiac diseases is provided on Table 2.

6. 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 [35]. 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 I_{Kur} 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.

In fact, modulation of microRNA function enlightens the creation of novel therapeutic tools in cardiac electrophysiology using miRNA biology. miRNA mimics can be used to increase beneficial miRNAs expression in disease settings, such as long QT or Brugada syndromes, respectively, whereas miRNA inhibitors can be administered to block microRNA activity that drive disease progression. Supporting evidences on this front have been already reported [47]. In this context, identification and validation of miRNA targets is essential for the development of miRNA-based therapeutics [190]. It is therefore

expected to soon see increasing evidence of the therapeutic application of microRNA-based approach in the context of cardiac arrhythmias.

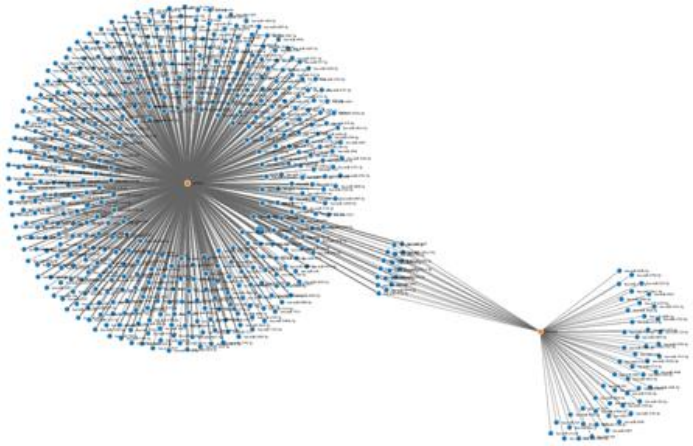

Figure 2. Plausible interactive networks of microRNA regulation on SCN5A and SCN10A as predicted using MirWalk algorithm.

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 I_{TO} current throughout the miR-200c/HMGB1 pathway [73], on LncRNA-LINC00472 acting as a miR-24 sponge and thus regulating RYR2 expression [99] and of CircITCH as a natural sponge of miR-330-5p, thereby upregulating SERCA2 [119] 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.

Author Contributions: Conceptualization, E.L.-V. and D.F., data curation E.L.-V. and D.F. Writing original draft preparation, E.L.-V. and D.F., Writing-review and editing, E.L.-V., A.A. and D.F. Funding adquisition, A.A. and D.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Consejeria de Transformaci n Econ mica, Industria, Conocimiento y Universidades of the Junta de Andalucia Regional Council, grant number CTS-446.

Conflicts of Interest: The authors declare no conflict of interest.

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