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MOUSE MODELS OF ARRHYTHMOGENIC CARDIOVASCULAR DISEASE: CHALLENGES AND OPPORTUNITIES

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Abstract

Arrhythmogenic cardiovascular disease is associated with significant morbidity and mortality and, in spite of therapeutic advances, remains an enormous public health burden. The scope of this problem motivates efforts to delineate the molecular, cellular and systemic mechanisms underlying increased arrhythmia risk in inherited and acquired cardiac and systemic disease. The mouse is used increasingly in these efforts owing to the ease with which genetic strategies can be exploited and mechanisms can be probed. The question then arises whether the mouse has proven to be a useful model system to delineate arrhythmogenic cardiovascular disease mechanisms. Rather than trying to provide a definite answer, the goal here is to consider the issues that arise when using mouse models and to highlight the opportunities.

Keywords

Sudden Cardiac Death; Long QT Syndrome; Short QT Syndrome; Brugada Syndrome; Dravet Syndrome; Wolf-Parkinson White Syndrome

Introduction

In spite of the clear progress in cardiac surgery, device and pharmacological therapies, and the resulting improvements in life span that have been realized in recent years, sudden death remains a major public health problem [1, 2]. In congenital arrhythmia syndromes [3–7], sudden death is often the first presentation, and familial hypertrophic cardiomyopathy is the most common cause of sudden death in apparently healthy children and young adults [8]. The situation with acquired cardiac disease is even more grim. Heart failure, for example, which afflicts more than 5 million adults in the United States alone, continues to be associated with markedly increased risk of ventricular arrhythmias and sudden cardiac death, and heart failure death rates continue to rise [1, 2, 9]. The mechanisms linking heart failure to increased arrhythmia and sudden death risk are poorly understood and, despite considerable attention and effort, risk stratifying patients remains an enormous challenge [10, 11]. In addition, approximately 2.5 million Americans suffer atrial fibrillation, which is associated with increased risk of stroke, heart failure, and death and, importantly, the

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incidence of atrial fibrillation increases dramatically with structural heart disease and with age [12, 13]. Further compounding the problem is the pandemic of obesity-related type 2 diabetes. In the US, approximately 60% of adults are overweight or obese, and cardiovascular disease is the leading cause of death in diabetes [14, 15]. With the obesity and type 2 diabetes epidemics and the population aging, the impact of cardiovascular disease on health care costs and the quality of life are staggering.

The cellular, molecular and systemic mechanisms linking congenital and structural heart disease, heart failure, atrial fibrillation, and derangements in systemic/cardiac metabolism to increased risk of arrhythmias and sudden death are poorly understood. There is consensus, however, that increased effort, focused on detailing disease progression and on delineating mechanisms that contribute to arrhythmogenic cardiovascular disease, is needed to provide new insights. Accomplishing this requires the development and application of appropriate molecular, cellular and systemic models that allow multiscale and multidisciplinary investigation and analyses. Over the years, a variety of experimental model systems have been developed for this purpose although, in the past two decades, the mouse has been used increasingly, primarily owing to the ease with which molecular genetic strategies can be exploited, functional assays can be completed, and molecular mechanisms can be probed. Evaluating the potential utility of the mouse as a model system for investigating congenital and acquired arrhythmogenic cardiovascular disease mechanisms first requires consideration of the electrophysiological properties of the mouse heart and how these compare with the human heart.

Myocardial Action Potential Waveforms and Underlying Ionic Currents

The mammalian heart is a rhythmic electromechanical pump, the functioning of which depends on action potential generation and propagation, followed by relaxation and a period of refractoriness until the next impulse is generated [16, 17]. Electrical activity in the myocardium is evident on the surface electrocardiogram (ECG), revealing the sequence of propagation through the atria (P wave) to the depolarization (QRS complex), followed by the repolarization (T wave), of the ventricles (Figure 1). Although the characteristic ECG features (P, QRS and T waves) in the mouse ECG are similar to those recorded in humans, there are rather striking differences (Figure 1). The T wave in the mouse, for example, is not well resolved (Figure 1) and the resting heart rate in the adult mouse is 600–700 beats per minute, approximately ten times faster than in the normal adult human [16, 17]. In addition, the durations and waveforms of action potentials in mouse and human atrial and ventricular myocytes are quite different (Figure 1). In human atrial and ventricular myocytes, the upstroke phase of the action potential is followed by a transient repolarization (phase 1) to a plateau phase (phase 2), whereas, in mouse atrial and ventricular cells, there is no clear plateau phase, and repolarization is rapid (Figure 1).

Myocardial action potential waveforms reflect the sequential activation and inactivation of voltage-gated inward Na^+ and Ca^{2+} , and outward K^+ , current carrying ion channels (Figure 2). Action potential waveforms are distinct in different regions of the heart owing primarily to differences in the K^+ channels expressed, and these differences contribute to the generation of normal cardiac rhythms. Conduction and the propagation of activity through the heart depend on electrical coupling between cells, coupling that is mediated by gap junction channels. In the diseased myocardium, action potential waveforms and conduction can change markedly, owing to changes in the functional expression of depolarizing Na^+ and Ca^{2+} , repolarizing K^+ , and/or gap junction, channels. Changes in channel expression or functioning, resulting from inherited or acquired disease, affect action potential repolarization and can lead to desynchronization and increased risk of life-threatening arrhythmias [17, 18].

Electrophysiological studies have detailed the properties of the Na^+ , Ca^{2+} and K^+ currents that generate cardiac action potentials, and molecular cloning has revealed a large number of pore forming (α) and accessory (β) subunits that contribute to the formation of these channels [17]. In addition, considerable progress has been made in defining the functional roles of the various channels and in identifying the α -subunits encoding these channels (Figure 2). Although there are multiple repolarizing K^+ currents in both human and mouse ventricular myocytes, there are some clear differences. The two prominent voltage-gated K^+ (Kv) currents in human ventricles, for example, I_{Kr} and I_{Ks} (Figure 2), are undetectable in adult mouse ventricular cells [17]. Rather, there are three distinct delayed rectifier currents, $\text{I}_{\text{K,slow1}}$, $\text{I}_{\text{K,slow2}}$ and I_{ss} , expressed in adult mouse ventricular myocytes. Mutations in the genes encoding Kv channel subunits, as well as changes in Kv channel properties or expression associated with acquired cardiac disease, are linked to cardiac arrhythmias [3, 7, 17].

Mouse Models of Congenital Human Ion Channelopathies and Arrhythmias

As noted above, although many large and small animal models of arrhythmogenic cardiovascular disease have been generated over the years, the mouse has been used increasingly primarily because of the ease with which transgenic and gene targeted strategies can be exploited and a number of mouse models of congenital human arrhythmia syndromes linked to defects in voltage-gated ion channels, often referred to as “ion channelopathies”, have been developed (19–21). Mutations in the *SCN5A* gene, which encodes the main cardiac voltage-gated Na^+ (Nav) channel α subunit, Nav1.5 , underlie several hereditary cardiac arrhythmias [3, 7]. Gain-of-function mutations in *SCN5A*, for example, are linked to type 3 Long QT syndrome (LQT3), whereas loss-of-function mutations are associated cardiac conduction diseases, Brugada syndrome, and sick sinus syndrome [3, 7], and the mouse (Table 1) has been used extensively to develop models of these Na^+ channelopathies [20, 22, 23]. Mouse models of Timothy Syndrome, linked to mutations in the gene (*CACNA1C*) encoding the predominant voltage-gated Ca^{2+} channel α subunit in the heart, have also been developed and applied [24–26] to study the neurological, as well as the cardiac, phenotypes associated with this syndrome.

Mice (*Scn5a*^{Δ/+}) heterozygous for a knock in of the LQT3 gain of function (ΔKPQ) deletion reportedly display action potential prolongation and increased spontaneous and inducible polymorphic ventricular arrhythmias (Table 1) and appear to represent a reasonable model of LQT3 [27, 28]. Similar to patients with loss of function mutations in *SCN5A*, mice (*Scn5a*^{+/-}) with heterozygous targeted disruption of *Scn5a*, display a Brugada like phenotype and conduction defects (Table 1). In addition, the phenotypic heterogeneity reported in the *Scn5a*^{+/-} model, that is also seen in patients, has been shown to reflect the variable expression of the wild type *Scn5a* allele [29]. A mouse model of Dravet Syndrome, with altered *Scn1a* (which encodes Nav1.1) expression, which appears to recapitulate a Sudden Unexplained Death in Epilepsy phenotype, was also recently described [30]. Interestingly, but unexpectedly, mice lacking the Nav channel accessory $\beta 1$ ($\text{Nav}\beta 1$) subunit were reported [31] to display marked ventricular action potential and QT prolongation (Table 1), observations that suggest $\text{Nav}\beta 1$ -mediated effects on repolarizing K^+ currents or, alternatively, electrical remodeling due to the loss of $\text{Nav}\beta 1$ and reduced Nav currents.

The genes, *KCNQ1* and *KCNH2* have been identified as loci of mutations in familial long QT syndromes 1 (LQT1) and 2 (LQT2), and, in addition, shown to encode the Kv α subunits, Kv7.1 and Kv11.1 , that generate cardiac I_{Ks} and I_{Kr} channels (17). Neither $\text{I}_{\text{Kr}}/\text{I}_{\text{Ks}}$, nor the Kv α subunits that encode these channels, *Kcnq1* and *Kcnh2*, is prominently expressed in adult mouse ventricular myocardium (Figure 2). Nevertheless, similar to the Na^+ channelopathies, considerable effort has been devoted to the application of transgenic

and targeted deletion strategies in mice to study K^+ channelopathies, and mice with altered expression of *Kcnq1* and *Kcnh2*, as well as of the (*Kcne1*) gene, which encodes the I_{Ks} channel accessory subunit, minK, have been generated and characterized [20]. Although there are some phenotypic differences in the consequences of the deletion of the *Kcne1* and *Kcnq1* genes in different mouse models [20], the cardiac effects are, overall, quite subtle (Table 1), as might be expected given that I_{Ks} is undetectable in adult mouse ventricles (Figure 2). Interestingly, in (*kcne2*^{-/-}) mice harboring a targeted disruption of the *kcne2* locus, a gene that has been linked in humans to both Long QT and Brugada Syndromes [17], multiple repolarizing K_v currents are affected, and ventricular action potential and QT prolongation (Table 1) are observed [32].

In several K_v channel transgenic and gene targeted mice that have been generated, ECG abnormalities, including QT prolongation, as well as increased inducibility of ventricular arrhythmias, have been described (Table 1) and, in some cases, the observed abnormalities structurally resemble those seen in humans. Although rare, quite dramatic ECG phenotypes and spontaneous arrhythmias have been reported in some K^+ channel transgenics. In the KCNQ1-isoform-2-expressing mouse, for example, QT prolongation, P wave abnormalities and Torsade de Pointes (Table 1) were reported. The severity of the cardiac phenotype was correlated with the amount of the mutant protein expressed, observations that suggest non-specific *in vivo* cardiac effects of transgenic protein “over-expression”. Overall, the incidence of spontaneous and/or inducible arrhythmias, particularly lethal arrhythmias that mimic those in humans, in mice with altered K^+ channel expression is very low (Table 1), observations that may reflect an inherent limitation of the mouse, owing perhaps to the small size of the heart and the rapid heart rate. This explanation seems unlikely, however, because ventricular arrhythmias and sudden death are observed in mice with cardiac restricted deletion of the cardiac gap junction channel protein, connexin 43, Cx-43 [33], observations interpreted as suggesting that conduction defects, alone or in combination with altered repolarization, are more influential in inducing arrhythmias than changes in repolarizing K^+ currents alone. Interestingly, it was also recently reported that lethal arrhythmias are observed in mice lacking the last 5 amino acids in the C terminus of Cx-43 in which gap junction coupling is preserved [34].

Additional studies in mice have focused on determining the molecular identities of the $K_v \alpha$ subunits encoding the delayed rectifier K^+ currents expressed in the mouse myocardium (Figure 1) and on exploring the functional consequences of the manipulation of these currents *in vivo* have also been reported (Table 1). A variety of cardiac K_v channel accessory subunits, including the $K_v \beta$, KChIP and DDPX subunits appear to contribute to the generation of native cardiac K_v channels [17], although the functional roles of these subunits have been less well studied than the $K_v \alpha$ subunits. It was reported [35], however, that the targeted deletion of KChIP2 results in increased susceptibility of ventricular arrhythmias and sudden death, although more recent studies [36] have failed to recapitulate these dramatic phenotypes (Table 1), perhaps reflecting the different genetic backgrounds used in these studies.

Other Mouse Models of Arrhythmogenic Cardiovascular Disease

In addition to the cardiac ion channelopathies, the mouse has also proven to be very useful in efforts to develop experimental models of other inherited [37–39], as well as acquired [40–43], arrhythmogenic cardiovascular diseases. Intracellular Ca^{2+} plays a pivotal role in electromechanical coupling in the mammalian heart and, as would be expected, derangements in the regulation of Ca^{2+} influx and intracellular Ca^{2+} are linked to congenital and acquired arrhythmias [4, 6], including congenital catecholaminergic polymorphic ventricular tachycardia (CPVT). Mutations in the cardiac ryanodine receptor and in cardiac

calsequestrin, the most abundant Ca^{2+} binding protein in the sarcoplasmic reticulum, have been linked to CPVT and mouse models harboring the human mutations have provided important cellular and systemic insights into the relationship(s) between alterations in sympathetic tone, intracellular Ca^{2+} handling and increased susceptibility to, and incidence of, lethal ventricular arrhythmias [37–39].

It was recently reported [44] that the activation of Notch signaling in the developing mouse myocardium is associated with ventricular preexcitation (Figure 3A), attributed to the presence of accessory pathways that allow the rapid conduction of electrical impulses directly from atria to ventricles, without the intrinsic delay characteristic of the atrioventricular node. The phenotype evident in these mice is strikingly similar, therefore, to Wolff-Parkinson-White syndrome, which is known to be caused by the presence of accessory pathways, and to result in increased risk of tachyarrhythmia, palpitations, syncope, and sudden death. Additional studies revealed that the inhibition of Notch signaling in the developing myocardium results in a hypoplastic atrioventricular and loss of the typical atrioventricular node conduction delay, attributed to the loss of the gap junction protein, connexin 30.2 [44]. In subsequent studies, Rentschler and colleagues [45] went on to demonstrate that increased Notch signaling directs developing ventricular myocytes to adopt an electrical phenotype that more closely resembles specialized conduction cells, specifically Purkinje cells (Figure 3B). Action potential waveforms recorded from ventricular myocytes isolated from animals with increased Notch signaling were distinct from those of normal, wild type ventricular cells and, indeed more closely resembled action potentials recorded from wild type Purkinje cells (Figure 3C). In addition, the expression levels of several transcripts associated with conduction cell lineage were shown to be increased in the ventricles of transgenic mouse with increased Notch signaling [45]. The timing of the observed effects is particularly interesting: although, at birth, conduction system markers were not increased globally in the ventricles of the animals with increased Notch signaling, these markers were observed outside the regions where conduction tissue is normally found, suggesting that increased Notch signaling results in electrical “reprogramming”.

Summary and Conclusions

Mouse models have been used increasingly over the past two decades to probe the cellular, molecular and systemic mechanisms involved in increasing the risk of potentially lethal ventricular arrhythmias in inherited and acquired cardiovascular diseases. Some of these models have proven to be much more useful than others in providing insights into human arrhythmogenic disease mechanisms. The (*Scn5a*) mouse models of the human *SCN5A*-related cardiac Nav channelopathies, including LQT3, Brugada and overlap syndromes, for example, have been found to recapitulate many of ECG and arrhythmia phenotypes (Table 1) that are observed in patients. In addition, in some cases, it has even been possible to explore the molecular determinants of heterogeneity in phenotypic penetrance of identified *SCN5A* mutations [29]. Nevertheless, it is clear that mouse models have limitations, some of which reflect the distinct electrophysiological properties of the mouse, as compared with the human, heart including the marked differences in size, heart rates and action potential waveforms (Figure 1). The impact of the various mouse models of the human cardiac Kv channelopathies, for example, has been limited, likely reflecting the marked differences in the Kv channels that underlie ventricular repolarization in human and mouse (Figure 2). In spite of these limitations, however, important insights into the relationships between individual K^+ channel subunits and functional K^+ currents, as well as about the mechanisms underlying the electrical remodeling observed in association with alterations in the expression or functioning of individual K^+ channel α and β subunits, have been provided through the application of *in vivo* molecular genetic strategies in the mouse. Recent studies

in the mouse are also providing the first insights into the programming and the reprogramming of electrical phenotypes in the heart. Together, these insights will guide the design, execution and interpretation of future experiments focused delineating the molecular, cellular and systemic mechanisms underlying electrical remodeling and reprogramming in the myocardium. The mouse is expected to be a widely used model system in these efforts.

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Highlights

ECG and action potential waveforms are markedly different in humans and mice.

Mouse models of *Scn5a* channelopathies recapitulate many aspects of human disease.

Distinct repolarization mechanisms limit mouse models of human Kv channelopathies.

Mouse models of Ca²⁺ dependent arrhythmias provide novel cellular insights.

Electrical remodeling and reprogramming mechanisms are increasingly probed in mice.

Figure 1. Schematic illustrating human and mouse ventricular (V) and atrial (A) action potential and ECG waveforms

Representative transmembrane action potentials are plotted above representative surface ECG recordings; P waves, QRS complexes and T waves are indicated. Note the marked differences in action potential and ECG waveforms and in the time base for the human versus mouse recordings.

Figure 2. Action potential waveforms and underlying ionic currents in human and mouse ventricular myocytes

Inward Na^+ and Ca^{++} , together with multiple outward K^+ current carrying ion channels, are co-expressed in human and mouse ventricular cells. Note the differences in the expression levels of some of the repolarizing K^+ currents, differences that contribute to the distinct action potential waveforms in human and mouse ventricular cells.

Figure 3. ECG abnormalities in mice and action potential remodeling with increased ventricular notch signaling

(A) Representative 6-lead ECG recordings and intracardiac electrograms from the right atrium and His bundle are shown from a wild type (control) mouse and a mouse (Notch*) with increased Notch signaling. Note the fused P wave and QRS complexes and the widened QRS complexes with delta wave on the surface ECG, as well as the fused atrial (A) and ventricular (V) electrograms in Notch* mice, indicative of AV conduction and ventricular preexcitation through the accessory pathway. (B) Representative action potentials recorded from EGFP-negative (EGFP⁻) and EGFP-positive (EGFP⁺) ventricular myocytes isolated from the hearts of (Notch*) mice with increased notch signaling in the myocardium.

Although the morphologies of the EGFP⁻ and EGFP⁺ cells are similar, action potential waveforms recorded in EGFP⁻ and EGFP⁺ cells are distinct: action potentials in EGFP⁻ cells resemble wild type ventricular myocyte action potentials, whereas action potentials in EGFP⁺ cells are prolonged, display a plateau and more closely resemble those recorded from native Purkinje cells. (C) Representative action potentials recorded from Purkinje cells isolated from (Cnnt2-EGFP⁺) mice [46] with EGFP expression in the cardiac conduction system driven by the contactin-2 promoter. (Figure adapted with permission from Rentschler et al., 2012 [45]).

Table 1
Phenotypic consequences of gene targeted alterations in cardiac voltage-gated Na⁺ and K⁺ Channels

Mouse	Modification	Strain	Current Affected	Cellular Phenotype	ECG Phenotype	Arrhythmias
<i>Scn5a</i> ^{+/-}	Exon 2 deletion	129Sv/J	↓I _{NaP}	ND	↑P, PR, and QRS	Yes
<i>Scn5a</i> ^{Δ/+}	ΔKPQ1505-1507 deletion	129Sv/J	↑I _{NaL}	↑APD	↑QT	Yes
<i>Scn5a</i> ^{L798insΔ/+}	Insertion	FVB/N	↓I _{NaP} ; ↑I _{NaL}	↑APD	↑PR, QT, and QRS	Yes
<i>hSCN5A-N1325S</i>	Tg/Point mutation	FVB/N	↑I _{NaL}	↑APD	↑QT	Yes
<i>Scn1b</i> ^{-/-}	Exon 3 deletion	C57BL6	↑I _{NaP} ; ↑I _{NaL}	↑APD	↑QT and RR	No
Kv4.2W362F	Tg/Point mutation	C57BL6	I _{to,f} eliminated	↑APD	↑QT	No
Kv4.2N	Tg/Truncation	C57BL6	↓I _{to,f} ; ↓I _{K1}	↑APD	ND	Yes
Kv4.2 ^{-/-}	Exon 1 deletion	FVB and C57BL6	I _{to,f} eliminated	↑APD	None	No
Kv1.4 ^{-/-}	1.4 deletion	C57BL6	I _{to,s} eliminated	No change	None	No
Kv4.2DN/Kv1.4 ^{-/-}	Tg in Kv1.4 ^{-/-}	C57/BL6	I _{to,i} and I _{to,s} eliminated	↑APD	↑QT	Rare
Kv1.1N206	Tg/Truncation at 216	FVB/N	I _{K,slow1} eliminated	↑APD	↑QT	Yes
Kv2.1N216	Tg/Truncation at 206	C57BL6	I _{K,slow2} eliminated	↑APD	↑QT	No
SWAP	Replace mouse Kv1.5 with rat Kv1.1	C57BL6	I _{K,slow1} eliminated	None	None	No
Kv1.1N116/ Kv2.1N206	Double Tg	C57BL6/FVB	I _{K,slow1} and I _{K,slow2} eliminated	↑APD	↑QT	Yes
Kv1.1N216/ Kv4.2W362F	Double Tg	C57BL6/FVB	I _{to,f} eliminated I _{K,slow1} eliminated	↑APD	↑QT	No
<i>Kcne1</i> ^{-/-}	Replace <i>Kcne1</i> with lac Z	129Sv/J	ND	ND	None	Yes
<i>Kcne2</i> ^{-/-}	<i>Kcne2</i> deletion	129Sv/J	↓I _{to,f} ; ↓I _{K,slow1}	↑APD	↑QT	No
<i>Kcng1</i> ^{-/-}	Exon 1 deletion	C57BL6	ND	ND	None	No
<i>Kcng1</i> ^{-/-}	Exon 2 deletion	C57BL6	ND	ND	↑QT, P, and T Wave	No
<i>KCNQ1</i> -isoform 2	Tg	FVB	↓I _{to,f} ; ↓I _{K1}	↑APD	↑QT Bradycardia	No
<i>KCNH2-G628S</i>	Tg	FVB	↓I _{Kr}	↑APD	None	No
<i>ERG1</i> ^{-/-}	Deletion	129Sv/J	ND	ND	ND	No
<i>ERG1B</i> ^{-/-}	Exon 1b deletion	Not reported	ND	ND	↑QT Bradycardia	ND
<i>KCHIP2</i> ^{-/-}	Exon 1 deletion	129Sv/J	I _{to,f} eliminated	↑APD	None	Yes
<i>KCHIP2</i> ^{-/-}	Exon 1 deletion	C57BL6	I _{to,f} eliminated	None	None	No
Kir2.1 ^{-/-}	Kir2.1 deletion	FVB	I _{K1} eliminated	↑APD	Bradycardia	ND

Mouse	Modification	Strain	Current Affected	Cellular Phenotype	ECG Phenotype	Arrhythmias
Kir2.2 ^{-/-}	Kir2.2 deletion	FVB	↓I _{K1}	None	None	No
Kir3.4 ^{-/-}	Exon 4 deletion	129Sv/1	I _{KACH} eliminated	None	Heart rate variability altered	No

Tg = Transgenic ND = Not Determined