Molecular and genetic basis of sudden cardiac death

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The abrupt cessation of effective cardiac function due to an aberrant heart rhythm can cause sudden and unexpected death at any age, a syndrome called sudden cardiac death (SCD). Annually, more than 300,000 cases of SCD occur in the United States alone, making this a major public health concern. Our current understanding of the mechanisms responsible for SCD has emerged from decades of basic science investigation into the normal electrophysiology of the heart, the molecular physiology of cardiac ion channels, fundamental cellular and tissue events associated with cardiac arrhythmias, and the molecular genetics of monogenic disorders of heart rhythm. This knowledge has helped shape the current diagnosis and treatment of inherited arrhythmia susceptibility syndromes associated with SCD and has provided a pathophysiological framework for understanding more complex conditions predisposing to this tragic event. This Review presents an overview of the molecular basis of SCD, with a focus on monogenic arrhythmia syndromes.

Introduction

When a person dies suddenly and unexpectedly from a suspected cardiovascular cause, the term sudden cardiac death (SCD) is used to classify the mortal event. SCD is frequently caused by an abrupt change in heart rhythm (arrhythmia), most often ventricular tachycardia (VT) or ventricular fibrillation (VF), that impairs cardiac pumping, thereby depriving vital organs of oxygenated blood. A brief episode of VT or VF may cause only momentary loss of consciousness (syncope), but death is the inevitable result of sustained VF in the absence of emergent medical care. Estimates of the annual SCD incidence vary but are generally in the range of 50–100 per 100,000 persons in industrialized nations (1). In the United States, previous estimates have been as high as 450,000 deaths per year (2), representing a large fraction of total mortality statistics largely reflect adult deaths in the setting of ischemic heart disease or heart failure, but children can also be susceptible to SCD in the context of certain genetic disorders.

Understanding the root causes of SCD has been an important research endeavor for several decades, and much progress has been made in defining the cellular, molecular, and genetic basis for ventricular arrhythmogenesis, the main pathophysiological provocateur of SCD (3). Mendelian (i.e., monogenic) syndromes predisposing to life-threatening ventricular arrhythmias in young adults and children are genetically heterogeneous, with more than 25 genes identified so far (Table 1). Molecular mechanisms related to these conditions involve membrane ion channels important for cardiomyocyte electrogenesis or regulation of intracellular Ca\(^{2+}\) homeostasis. By contrast, the genetic risk for SCD in older adults is more complex, with few if any unifying hypotheses about molecular mechanisms, although some overlap is observed with susceptibility to monogenic arrhythmia. Furthermore, the respective contributions of genetic and acquired factors to pathogenesis vary along the spectrum of age, with inborn errors having the greatest impact on SCD risk in younger subjects and acquired factors dominating risk in older subjects.

This Review presents an overview of the molecular basis of SCD, with a focus on monogenic arrhythmia syndromes. The emerging picture of SCD risk as a complex genetic trait in older subjects has been reviewed elsewhere (4, 5). An initial brief summary of basic arrhythmia mechanisms at the cellular and tissue levels will provide a framework for presenting the molecular underpinnings.

Ventricular arrhythmia mechanisms

The normal initiation and orderly propagation of the cardiac impulse through the heart requires a tightly orchestrated sequence of changes in ionic currents that sum to produce the dynamic and phasic change in membrane potential referred to as the cardiac action potential (Figure 1). Abnormal properties of ionic currents can cause electrical disorder and lead to aberrant impulse generation or propagation. Consequently, rapid and sometimes chaotic electrical activity in the ventricles ensues, manifesting as either VT or VF that can lead to SCD. In a simplistic model, there are two major prerequisites for arrhythmic events: a vulnerable myocardial substrate and a trigger.

Myocardial conditions that increase risk for arrhythmias include structural (anatomical) and functional causes of heterogeneous conduction velocity that disrupt the normal orderly propagation of action potential waves through the ventricles (6). Heterogeneous conduction can predispose to the emergence of spiral waves, impulses that travel in a circular pattern around an anatomic barrier, as in ischemic or scarred myocardium, or around a point of reentry known as a rotor in non-ischemic and structurally normal myocardium (7). If uninterrupted, rhythmic spiral wave propagation in the ventricles will be associated with VT, but degeneration or fragmentation into smaller wavelets creates the more chaotic impulse movement associated with VF. Transmural dispersion of repolarization can also predispose to reentry. Normally, there is heterogeneity of action potential duration across the wall of the ventricles, with shorter action potentials occurring in the epicardial layer. This phenomenon arises from a more prominent epicardial transient outward current (\(I_{\text{to}}\)). Exaggeration of this transmural heterogeneity can create circumstances in which the fully repolarized epicardium can be reexcited by depolarized mid-myocardial and endocardial layers (8, 9).

Conflict of interest: The author has declared that no conflict of interest exists.

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### Table 1
Genes involved in monogenic causes of SCD

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A focal ectopic impulse generated in the ventricles can trigger the initiation of spiral waves and cause reentrant arrhythmias. At the cellular level, early afterdepolarizations (EADs) or delayed afterdepolarizations (DADs) provide the most common mechanisms for ectopic excitation. EADs arise during the plateau phase of the cardiac action potential, whereas DADs emerge after completion of an action potential (Figure 2 and refs. 10, 11). Both events occur because of aberrant depolarizing ionic currents. In the case of EADs, increased activation of voltage-gated (L-type) Ca\(^{2+}\) channels or persistent activation of voltage-gated Na\(^+\) channels is the usual mechanisms. By contrast, DADs arise from spontaneous intracellular Ca\(^{2+}\) release and efflux of Ca\(^{2+}\) through the electrogenic Na\(^+\)/Ca\(^{2+}\) exchanger (NCX; stoichiometry 3Na\(^+\):1Ca\(^{2+}\)), evoking a transient inward Na\(^+\) current aC with a small amount of residual I\(_{\text{Na}}\) and emerging outward currents carried by K\(^+\) channels. Activation of two types of K\(^+\) currents (I\(_{\text{Kr}}\), I\(_{\text{Ks}}\)) in concert with inactivation of Ca\(^{2+}\) channels tips the balance in favor of the outward current, thereby promoting phase 3 repolarization. Finally, the inward rectifying K\(^+\) current (I\(_{\text{K1}}\)) finishes the job of repolarizing myocyte membranes. Other electrogenic transporters (NCX, Na\(^+\)/K\(^+\) ATPase) are involved in maintaining intracellular ionic homeostasis in the face of large ion fluxes accompanying each action potential.

Many ion channels involved with the generation and propagation of cardiac action potentials are regulated by several factors, most notably β-adrenergic stimulation. In particular, during exercise or stress in which the sympathetic nervous system is activated (fight or flight response), heart rate acceleration requires shortening of the action potential duration, and this is accomplished in part by activating I\(_{\text{Ks}}\) through a CAMP-dependent mechanism. Sympathetic stimulation also enhances contractility of the heart, mainly through augmentation of Ca\(^{2+}\) influx (activation of I\(_{\text{Ca}}\)) and increased loading of the SR so that more Ca\(^{2+}\) can be released intracellularly during systole.

**Cardiac action potential**

The generation and propagation of action potentials in heart muscle as well as excitation-contraction coupling are physiological events dependent upon a symphony of ion channels acting in concert with many associated regulatory or interacting proteins. Ion channels are ubiquitous proteins that confer selective ionic permeability to cell membranes. Voltage-gated ion channels are opened and closed by changes in membrane potential, whereas ligand-gated ion channels require binding of intracellular or extracellular molecules to open an ionic pore. Voltage-gated ion channels with selective permeability for Na\(^+\), K\(^+\), and Ca\(^{2+}\) ions feature prominently in normal cardiac electrophysiology and in the molecular pathogenesis of monogenic disorders predisposing to SCD (Table 1).

**Monogenic causes of SCD**

Two categories of monogenic heart disease predispose to SCD. These are genetic disorders of heart rhythm and familial cardiomyopathy. Cardiomyopathy is discussed in depth elsewhere in this Review series (13), and therefore the focus here will be on genetic arrhythmia susceptibility. Although rare, these syndromes have been tractable at the molecular level, and nearly two decades of research have uncovered molecular mechanisms that may be shared with more common acquired conditions. The genes responsible for congenital arrhythmia syndromes for the most part encode either ion channel subunits or proteins that interact with ion channels (Table 1).

Rare genetic conditions known to predispose to SCD in children and young adults include the congenital long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BrS),
A

EAD

B

ECG from a typical polymorphic VT (also known as torsades de pointes), which is associated with EADs. (C) Illustration of a DAD arising after completion of action potential repolarization. DADs are commonly due to spontaneous intracellular Ca$^{2+}$ release and efflux of Ca$^{2+}$ through the electrogenic NCX (stoichiometry 3Na$^+:1$Ca$^{2+}$), which generates a transient $I_{\text{Na}}$. (D) ECG of VF, which is associated with DADs.

Figure 2

Afterdepolarizations and ventricular arrhythmias. EADs and DADs occur due to dysregulation of depolarizing ionic currents. (A) EAD illustrated in the context of prolonged action potential duration. EADs typically result from increased activation of voltage-gated (L-type) Ca$^{2+}$ channels or persistent activation of voltage-gated Na$^+$ channels. (B) ECG from a typical polymorphic VT (also known as torsades de pointes), which is associated with EADs. (C) Illustration of a DAD arising after completion of action potential repolarization. DADs are commonly due to spontaneous intracellular Ca$^{2+}$ release and efflux of Ca$^{2+}$ through the electrogenic NCX (stoichiometry 3Na$^+:1$Ca$^{2+}$), which generates a transient $I_{\text{Na}}$. (D) ECG of VF, which is associated with DADs.

review series

idiopathic VF, and catecholaminergic polymorphic VT (CPVT).

Three general mechanisms responsible for arrhythmia susceptibility have been elucidated in these disorders: abnormal repolarization (LQTS, SQTS, BrS), slow ventricular conduction (BrS), and aberrant intracellular Ca$^{2+}$ homeostasis (CPVT).

Congenital LQTS. The QT interval measured by standard surface ECG provides a surrogate measurement of the average ventricular action potential duration. Both a prolonged or shortened QT interval indicates an increased risk of life-threatening cardiac arrhythmias (14, 15). Congenital LQTS is characterized clinically by an increased risk of potentially fatal ventricular arrhythmias, especially torsades de pointes (16), manifesting as syncope, cardiac arrest, and SCD in otherwise healthy young adults and children. The syndrome is most often transmitted in families as an autosomal dominant trait (Romano-Ward syndrome) and less commonly as an autosomal recessive disease combined with deafness (Jervell and Lange-Nielsen syndrome). Autosomal dominant LQTS occurs in approximately 1 in 2,500 live births (17).

LQTS is genetically heterogeneous and can be caused by mutations in several genes encoding voltage-gated K$^+$ channel subunits ($KCNQ1$, $KCNH2$, $KCNE1$, $KCNE2$) (18–23), voltage-gated Na$^+$ channel subunits ($SCN5A$, $SCN4B$) (24, 25), an L-type Ca$^{2+}$ channel ($CACNA1C$) (26), inwardly rectifying K$^+$ channels ($KCNN3$, $KCNN4$, $KCNN5$) (27, 28), and various channel-interacting proteins ($ANK2$, $CAV3$, $AKAP9$, $SNTA1$) (29–32).

The most common genetic subtype of LQTS, LQT1, is caused by mutations in $KCNQ1$, a gene encoding the pore-forming subunit of the voltage-gated K$^+$ channel (Kv7.1) responsible for $I_{\text{Ks}}$ (20). Mutations in $KCNH2$, which encodes HERG (Kv11.1), the voltage-gated K$^+$ channel responsible for $I_{\text{Kr}}$, cause the LQT2 variant and account for the second largest proportion of LQTS cases (19, 33).

Heterozygous mutations in either $KCNQ1$ or $KCNH2$ lead to loss of function and can exert dominant-negative effects on the wild-type (non-mutant) allele. Loss of function of either Kv7.1 or HERG channels will reduce $I_{\text{Ks}}$ or $I_{\text{Kr}}$, respectively, causing delayed repolarization and prolonged ventricular action potential duration. During sympathetic activation, failure to augment $I_{\text{Ks}}$, during heart rate acceleration further exposes impaired repolarization and explains why LQT1 patients are most prone to arrhythmic events during exercise and emotional stress. Mutations in $KCN1$ and $AKAP9$ (encoding the A-kinase anchor protein also known as yotiao) exert similar functional effects on $I_{\text{Kr}}$, but are much less common (31, 33). Similarly, $KCN2$ mutations associated with LQTS may disrupt HERG function and reduce $I_{\text{Ks}}$, but sometimes only during pharmacological suppression of this current (22, 34).

In autosomal-dominant LQTS, mutations in $KCNQ1$ and $KCNH2$ may exert dominant-negative effects on the respective wild-type allele. Dominant-negative effects are best explained by the formation of dysfunctional tetrameric channel complexes with mixtures of wild-type and mutant subunits. Recessive $KCNQ1$ and $KCNE1$ mutations are responsible for Jervell and Lange-Nielsen syndrome (21, 23, 35) but do not exhibit dominant-negative effects, most likely because mutant proteins are not stable or do not form heteromultimers with wild-type subunits.

Impaired trafficking of mutant subunits is a common in vitro observation for $KCNH2$ mutations (36, 37). For some $KCNH2$ mutations, impaired trafficking can be corrected pharmacologically in heterologous cells (38), thus stimulating interest in this approach for therapy of LQT2. Modeling the effects of human $KCNQ1$ and $KCNH2$ mutations in vivo (e.g., genetically modified mice) have been challenging because of substantial differences in repolarizing currents in mouse heart. However, recent prog-
persistent Na disrupts the normal physiological balance of inward and outward currents flowing during the plateau phase of the cardiac action potential, causing delayed repolarization (44). Other alleles that encode pro-SNTA1 or KCNH2 mutations that reproduce KCNJ2 mutations reduce IK1 and cause prolongation of the action potential duration, with increased propensity for re-entrant arrhythmias despite lack of measurable IKr (44). Selective block of persistent IKs by certain anti-arrhythmic agents (e.g., mexiletine) or the anti-angina drug ranolazine may offer targeted therapy for LQT3 mutations (45–48).

Acquired LQTS is more common than congenital LQTS but shares similar pathophysiological mechanisms. Drug-induced LQTS (diLQTS), the most common form of acquired LQTS, occurs when cardiac or non-cardiac drugs block HERG channels, suppress IKr, and cause delayed repolarization (49). A genetic predisposition to diLQTS has been hypothesized, and this notion has received support from genetic association studies (50, 51). A common KCNE1 variant (D85N) carried by 1%–2% of the general population is overrepresented among diLQTS cases (52). The variant confers a partial loss-of-function upon IKs and causes a condition referred to as reduced repolarization reserve that predisposes to overt LQTS upon collateral inhibition of IKs (53). Anecdotal evidence also suggests that latent congenital LQTS may be unmasked by HERG-blocking drugs (54, 55) or other physiological provocations such as acute myocardial infarction (56).

**Syndromic LQTS: Andersen and Timothy syndromes.** In addition to Jervell and Lange-Nielsen syndrome, two other LQTS subtypes have prominent extracardiac manifestations. Andersen syndrome is an autosomal dominant disorder characterized by ventricular arrhythmias, periodic paralysis, and dysmorphic facial and skeletal features (27, 57). Considerable phenotypic variability exists among people diagnosed with Andersen syndrome, with many subjects exhibiting only one or two clinical features (58, 59). Although ventricular arrhythmia can be a prominent feature, this only rarely precipitates SCD (60).

Andersen syndrome is associated with mutations in KCNJ2 encoding the Kir2.1 inward rectifier K+ channel (27, 61, 62) that is responsible for the main component of IKr, an important current driving phase 3 repolarization (63). Dominant-negative, loss-of-function KCNJ2 mutations reduce IKr and cause prolongation of the action potential duration, with increased propensity for re-entrant arrhythmias (62, 64, 65). Some identified KCNJ2 mutations are predicted to affect residues important for the regulation of Kir2.1 channel activity by phosphatidylinositol 4,5-bisphosphate (66). Other alleles impair trafficking of the channel to the plasma membrane (67, 68). Previous investigation of mice with homozygous deletion of Kcnj2 demonstrated premature death secondary to cleft palate but no overt ventricular arrhythmias despite lack of measurable IKr in cardiac myocytes (64, 69). By contrast, in vitro suppression of IKr in isolated canine left ventricle caused delayed action potential repolarization, increased transmural dispersion of repolarization, and polymorphic VT resembling cardiac features of Andersen syndrome (70, 71).
In Timothy syndrome, mutations in CACNA1C, which encodes the voltage-gated Ca\(^{2+}\) channel pore-forming subunit (Ca\(_V\)), cause a complex phenotype including cardiac arrhythmia, syndactyly, and autism spectrum disorder (26). The syndrome exhibits sporadic occurrence as opposed to Mendelian inheritance, but a candidate gene survey demonstrated a common heterozygous mutation (G406R) in CACNA1C consistent with either de novo mutagenesis or parental mosaicism (26). A second mutation (G402S) was subsequently discovered (72). Both mutations occur within one of two mutually exclusive exons (exons 8 or 8A) present in alternatively spliced CACNA1C transcripts. Functionally, both mutations cause substantial impairment of channel inactivation, predicting an increased Ca\(^{2+}\) current during the plateau phase of the action potential (26, 72). Selective impairment of voltage-dependent inactivation rather than Ca\(^{2+}\)-dependent inactivation may be the main functional disturbance (73). This gain-of-function defect leads to increased Ca\(^{2+}\) entry and activation of calmodulin-dependent kinase II, stimulating a proarrhythmic cascade in isolated rabbit ventricular myocytes (74). Mice with heterozygous or homozygous expression of a Timothy syndrome mutation are not viable.

SQTS. Another disorder of repolarization, the SQTS, was described more recently and appears to be much rarer than LQTS (75). As in LQTS, subjects with SQTS can be stricken with life-threatening ventricular arrhythmias and SCD, often during childhood. Mutations in six different genes encoding either K\(^+\) channel (KCNQ1, KCNH2, KCNJ2) (76–78) or Ca\(^{2+}\) channel (CACNA1C, CACNB2, CACNA2D1) (79, 80) subunits have been associated with this phenotype. Many of these SQTS genes are the same as those implicated in LQTS, but the functional consequence of mutations is opposite. Mutations in K\(^+\) channels encoded by KCNH2 and KCNQ1 that cause SQTS exhibit gain-of-function effects predicted to enhance repolarizing power and shorten action potential duration (76, 77), effects that are modeled in zebrafish carrying mutant zERG channels with altered gating properties (81). By contrast, mutations in genes encoding Ca\(^{2+}\) channel subunits exhibit loss of function (79, 80). Mutations in KCNJ2 also confer a gain of function that for some alleles stems from unique biophysical behaviors, such as loss of inward rectification (82).

BrS. Individuals with BrS have an increased risk for potentially lethal ventricular arrhythmias usually occurring during sleep, but in the absence of myocardial ischemia, electrolyte abnormalities or structural heart disease (83). Individuals with the disease may exhibit a characteristic baseline ECG pattern consisting of ST elevation in the right precordial leads, apparent right bundle branch block, but normal QT intervals. Administration of Na\(^+\) channel blocking agents (e.g., procainamide, flecainide, ajmaline) (84) and fever (85) may unmask this ECG pattern in latent cases. A family history of unexplained sudden death is typical. The sudden unexplained death syndrome is clinically similar to BrS and causes sudden death, typically during sleep, in young and middle-aged males, with a higher prevalence in individuals from Southeast Asian countries (86–88). Inheritance is autosomal dominant with incomplete and often low penetrance and a substantial male predominance. One attractive hypothesis to explain incomplete penetrance in BrS is the existence of genetic modifiers that may be common variants in SCN5A or other genes (89–91).

Mutations in SCN5A account for less than 30% of BrS cases with known genotypes. Reduced \(I_{Na}\) is the primary pathophysiological mechanism due to loss-of-function mutations including frame-shifts, splice site defects, or premature stop codons (92, 93) that are predicted to encode nonfunctional Na\(^+\) channels. Also, some missense mutations have been demonstrated to be nonfunctional either because of impaired protein trafficking to the cell membrane or presumed disruption of ion conductance (94–96). Other missense mutations are dysfunctional, with biophysical defects predicted to reduce channel availability such as altered voltage dependence of activation, more rapid fast inactivation, and enhanced slow inactivation (97–99). Reduced \(I_{Na}\) may also be the consequence of mutations in other genes that less frequently cause BrS, including those encoding Na\(^+\) channel β subunits (SCN1B, SCN3B) (100, 101) or glycerol-3-phosphate dehydrogenase 1-like
An NADH/NAD+ imbalance that can activate protein kinase C by reducing enzymatic activity of mutant GPD1L is associated with the redox state of the cell (103, 104). Specifically, reduced Na+ current is predicted to exaggerate differences in action potential duration between the inner (endocardium) and outer (epicardium) layers of ventricular muscle (8, 9). These differences occur because of an unequal distribution of $I_{Na}$, which is more prominent in the epicardial layer and contributes to the characteristic spike and dome shape of the cardiac action potential. Reduced $I_{Na}$ causes disproportionate shortening of epicardial action potentials because of unopposed $I_{Na}$, leading to an exaggerated transmural dispersion of repolarization, a substrate promoting reentrant arrhythmias. This mechanism is supported by elegant work using the canine ventricular wedge model (8, 9). The second hypothesis posits that the main effect of reduced myocardial $I_{Na}$ is slowing of impulse conduction in the right ventricle and delayed activation of the right ventricular outflow tract (RVOT) (108–111). This mechanism has gained support primarily from clinical observations including electroanatomic mapping studies (112, 113) and the observed therapeutic benefit of epicardial ablation over the RVOT (114). Heterozygous Scn5a knockout mice (Scn5a−/+) have provided an animal model of BrS (115–117). Whether these two hypotheses are mutually exclusive or whether all cases of BrS originate by the same pathophysiological mechanism remains unclear.

**Summary and future directions**

Fundamental molecular and genetic mechanisms of SCD have been elucidated by investigations of rare monogenic disorders of heart rhythm. Despite the identification of more than 25 causal genes, there remain many subjects with inherited arrhythmia susceptibility who do not have mutations, which suggests that other, unidentified genes exist. Newer strategies such as exome sequencing may be valuable to uncover additional molecular etiologies. Efforts to understand mechanisms responsible for incomplete penetrance, including identification of modifier genes, will also contribute to deciphering the complex relationships between genotype and phenotype. Finally, better disease models such as cardiomyocytes derived from human-induced pluripotent stem cells created from patients with monogenic disorders predisposing to SCD, as described elsewhere in this Review series (130), may also help advance our understanding of SCD pathophysiology and inspire new therapeutic approaches.

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