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SPOTLIGHT REVIEW

Genetic basis and molecular biology of cardiac arrhythmias in cardiomyopathies

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Abstract

Cardiac arrhythmias are common, often the first, and sometimes the life-threatening manifestations of hereditary cardiomyopathies. Pathogenic variants in several genes known to cause hereditary cardiac arrhythmias have also been identified in the sporadic cases and small families with cardiomyopathies. These findings suggest a shared genetic aetiology of a subset of hereditary cardiomyopathies and cardiac arrhythmias. The concept of a shared genetic aetiology is in accord with the complex and exquisite interplays that exist between the ion currents and cardiac mechanical function. However, neither the causal role of cardiac arrhythmias genes in cardiomyopathies is well established nor the causal role of cardiomyopathy genes in arrhythmias. On the contrary, secondary changes in ion currents, such as post-translational modifications, are common and contributors to the pathogenesis of arrhythmias in cardiomyopathies through altering biophysical and functional properties of the ion channels. Moreover, structural changes, such as cardiac hypertrophy, dilatation, and fibrosis provide a pro-arrhythmic substrate in hereditary cardiomyopathies. Genetic basis and molecular biology of cardiac arrhythmias in hereditary cardiomyopathies are discussed.

Keywords Genetics • Cardiomyopathy • Arrhythmias • Ion channels • Electrophysiology • Sudden death

This article is part of the Spotlight Issue on Inherited Conditions of Arrhythmia.

1. Introduction

Cardiac arrhythmias are common and central features of hereditary cardiomyopathies, regardless of whether the cardiomyopathy is caused by a genetic mutation (or pathogenic variant) affecting myocyte structural proteins or is secondary to a defect in another component of myocytes. Throughout this review, the term mutation is used when evidence for causality is robust. Otherwise, the term pathogenic variant is used to describe genetic variants that are associated with the phenotype. Hereditary cardiomyopathies by definition are considered primary diseases of the myocardium and more specifically, cardiac myocytes. The term cardiomyopathy, however, is loosely applied to various forms of advanced heart failure resulting from secondary causes, such as coronary artery disease (CAD). For clarity, throughout this review, the term cardiomyopathy is used to describe primary diseases of cardiac myocytes and not heart failure secondary to external causes, such as CAD or loading conditions. Likewise, primary ion channel disorders or channelopathies are not considered as cardiomyopathies and are not covered in this review. Primary arrhythmogenic diseases are discussed in other articles in the spotlight issue. To avoid ambiguity in nomenclature, HUGO nomenclature is used to describe gene names (human genes all in capital letters and *italics*). Proteins are named as their corresponding genes in capital letters but not in *italics*.

2. An overview of hereditary cardiomyopathies

Common forms of hereditary cardiomyopathies are categorized according to their phenotypic features, as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic cardiomyopathy (ACM). Other uncommon forms of hereditary cardiomyopathies include restrictive cardiomyopathy (RCM), left ventricular non-

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compaction cardiomyopathy (LVNC), amyloid cardiomyopathy, among others (*Figure 1*).[1] Only common forms are discussed.

2.1 Hypertrophic cardiomyopathy

HCM is characterized by unexplained cardiac hypertrophy, a small left ventricular (LV) cavity, and a preserved or increased LV ejection fraction (EF) (reviewed in Ref.[2]). A notable phenotypic feature of HCM is the presence of LV outflow tract obstruction, which is detected at rest in approximately a quarter of patients and could be provoked with exercise or adrenergic stimulation in one-third of the patients. HCM is a major cause of sudden cardiac death (SCD) in the young.[3–5] The death is typically due to ventricular fibrillation.

Mutations in genes encoding sarcomere proteins are the main causes, while mutations in another two dozen genes have been associated with HCM. *MYH7* and *MYBPC3*, coding for myosin heavy chain 7 (or β myosin heavy chain) and myosin-binding protein C, respectively, are the two most common causal genes for HC (reviewed in Ref.[2]). Approximately 40% of HCM is caused by mutations in one of these two genes. *TNNT2* gene-encoding cardiac troponin T is the third most common causal gene but is responsible for <5% of the HCM cases. Other uncommon causal genes include *TPM1* (a-tropomyosin), *TNNI3* (cardiac troponin I), *ACTC1* (cardiac α-actin), *MYL2* (myosin light chain), *MYL3* (myosin light chain 3), and *CSRP3* (muscle LIM protein). Collectively, all known causal genes account for ∼50–60% of the HCM cases. The remaining causal genes have not been identified yet. Overall, the prevalence of each specific mutation in HCM is low, as the mutations are rare and often private. There is no clear genotype–phenotype correlation in HCM.

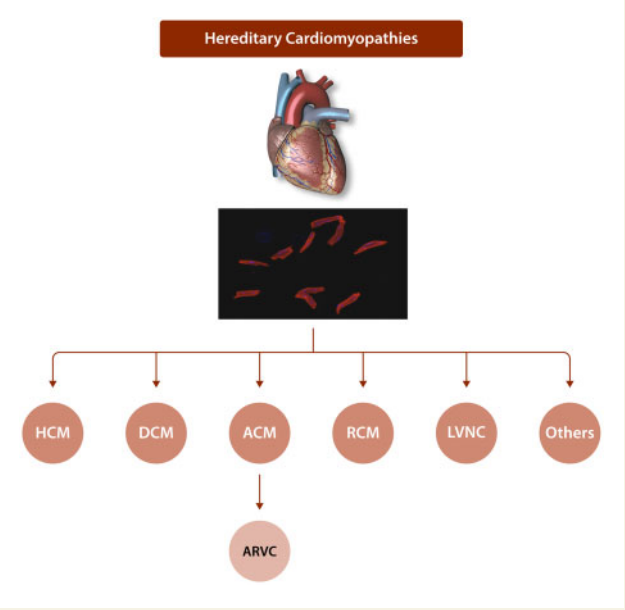

Figure 1 Classification of hereditary cardiomyopathies. Major forms for hereditary cardiomyopathies, which are classified based on their morphological and physiological features, are depicted. Adult cardiac myocytes are shown in the background to indicate that hereditary cardiomyopathies are primary disorders of cardiac myocytes.

2.2 Dilated cardiomyopathy

DCM is characterized by LV dilatation with an end-diastolic diameter of >2.7 cm/m^2 and a reduced LVEF of <45% (reviewed in Ref.[6]). Patients with DCM typically present with symptoms of heart failure but are often asymptomatic or exhibit reduced exercise tolerance in the early stages of the disease. Cardiac arrhythmias and SCD are typically the late manifestations of the disease and are absent in the early stages of DCM. Clinical manifestations of DCM commonly present in the third and fourth decades of life.

DCM is familial in about half of the patients and exhibits an autosomal-dominant mode of inheritance. DCM occasionally manifests as an X-linked disease, such as in Duchenne and Becker muscular dystrophies and Emery-Dreifuss syndrome. DCM is a genetically heterogeneous disease and mutations in over 50 genes have been associated with DCM.[6] *TTN*, encoding the giant sarcomere protein titin, is the most common causal gene being responsible for ∼20% of the DCM cases.[7] Mutations in *MYH7*, *TNNT2*, *ACTC1* are also important, albeit uncommon, causes of DCM, indicating a partially shared genetic basis for the two common forms of hereditary cardiomyopathies, namely HCM and DCM. Overall, the majority of the known DCM genes code for cytoskeletal proteins.

A subset of DCM is caused by mutations in the *LMNA* gene, which encodes the nuclear inner membrane protein lamin A/C (LMNA). The phenotype, in addition to DCM, is characterized by chronotropic insufficiency, cardiac conduction defects, bradycardia, atrial fibrillation, and ventricular arrhythmias.[8] Another subset of DCM is caused by mutations leading to cytoplasmic protein aggregation (proteotoxicity), including mutations in *DES*, encoding intermediary filament desmin, and *CRYAB*, encoding chaperon protein α/B-crystallin.[9] More recently, *RBM20* coding for RNA-binding motif protein 20 has emerged as an important cause of DCM.[10] RBM20 protein regulates RNA splicing and targets sarcomere genes among others, leading to their dysregulated expressions.

2.3 Arrhythmogenic cardiomyopathy

ACM is an enigmatic form of hereditary cardiomyopathies, whose cardinal manifestations are ventricular arrhythmias, which often are the first manifestation of the disease preceding pathological and functional abnormalities; SCD, and refractory heart failure (reviewed in Ref.[11]). ACM is an important cause of SCD in the young.[12–14] Both ventricles are typically involved but a subgroup of ACM classically manifests with predominant involvement of the right ventricle, particularly in the early stages, manifesting with cardiac arrhythmias originating from the right ventricle and fibro-fatty infiltration of the right ventricular myocardium. This subgroup is referred to arrhythmogenic right ventricular cardiomyopathy (ARVC).[13] An LV-dominant form of ACM also has been described.[15] The clinical phenotype of ARVC is also notable for the characteristic electrocardiographic findings including an epsilon wave, depolarization, and repolarization abnormalities in the right precordial leads, which are present in a subset of patients with ACM.[16,17]

The causal genes for ACM have been partially identified and code for protein constituents of desmosomes, members of the intercalated discs (IDs) (reviewed in Ref.[11]). IDs are responsible for maintaining mechanical integrity of the myocardium and are signalling hubs for mechano-sensing, such as the Hippo and the canonical WNT signalling pathways, which are dysregulated in ACM.[18,19] Mutations in *PKP2* gene coding for desmosome protein plakophilin 2 are the most common causes of ACM. Likewise, mutations in *DSP*-encoding desmoplakin, *JUP*-encoding junction protein plakoglobin, *DSC2*-encoding desmocllin 2, and *DSG2*-encoding desmoglein 2 are known to cause ACM. Mutations in several other genes are also implicated in ACM, including *TMEM43* gene coding for

transmembrane protein 43, *PLN* coding for phospholamban, *FLNC*-encoding filamin C, and *TTN* coding for titin. Mutations in the known genes are found in ~40–50% of the ACM cases.

2.4 Others

Genetic basis of other forms of hereditary cardiomyopathies, such as RCM and LVNC is not discussed, suffice it to state that there is a partially shared genetic aetiology among hereditary cardiomyopathies, as mutations in sarcomere genes are also associated with RCM and LVNC.

2.5 Pathogenesis of hereditary cardiomyopathies

The primary defect in hereditary cardiomyopathies, namely the mutation, provides the stimulus for phenotypic expression of the disease. The mutation often affects interactions of the mutant protein with its interactome. The interactome might include proteins that are involved in cardiac conduction and arrhythmias. The early phenotypic responses to altered protein function commonly entails dysregulation of gene expression, altering various biological and functional pathways within the cardiac myocytes. A subset of the dysregulated genes code for proteins that are secreted from cells (secretome) and function as paracrine factors. These paracrine factors, emanating from cardiac myocytes, not only affect cardiac myocytes (through autocrine mechanisms) but also other cell types in the heart, such as fibroblasts and endothelial cells, through paracrine mechanisms. Collectively, the molecular phenotypes lead to functional and structural dysregulation of multiple cell types in cardiomyopathies, particularly in advanced stages of the disease. Therefore, although cardiomyopathies are primary diseases of cardiac myocytes, the phenotype is the consequences of complex interactions among multiple cardiac cell types, through paracrine effects, protein–protein interactions, and other mechanisms. As regards cardiac conduction and arrhythmias, the prevailing data point to cardiac myocytes and cardiac conduction cells as the cell sources of cardiac conduction defects and arrhythmias in cardiomyopathies.

3. Prevalence of cardiac arrhythmias in hereditary cardiomyopathies

3.1 Arrhythmogenic cardiomyopathy

Cardiac arrhythmias are relatively common and often the dangerous manifestations of cardiomyopathies. ACM is the prototypic form of cardiomyopathies, whose cardinal and typically the first manifestation is ventricular arrhythmia.[20,21] Ventricular arrhythmias in ACM occur early, prior to, and typically in the absence of discernible cardiac dysfunction. This is in contrast to DCM or ischaemic heart disease, wherein ventricular arrhythmias typically manifest late in the course of the disease and often in the context of heart failure. While early ventricular arrhythmias are the common features of ACM, ventricular arrhythmias also occur late in advanced stages of ACM in conjunction with cardiac dysfunction, as in DCM. Approximately half of the patients with the classic form of ACM, namely ARVC, exhibit non-sustained ventricular tachycardia (NSVT) and approximately one-third show sustained ventricular tachycardia (VT) upon initial evaluation.[22] The incidence of sustained ventricular arrhythmias in patients with ACM is ~5% per year.[22] Male patients are at a higher risk of future ventricular arrhythmias, as are those with a history of syncope and prior ventricular arrhythmias as well as cardiac dysfunction.[22] Atrial arrhythmias are also common and present in up to half of the patients with ACM, typically in those with atrial and right ventricular enlargement.[23,24]

3.2 Hypertrophic cardiomyopathy

Cardiac arrhythmias are also common in HCM, typically occur in the context of clinical and pathological phenotypes of HCM and seldom are the sole manifestations. Approximately a quarter of patients with HCM exhibit NSVT in initial evaluation.[25,26] Sustained VT is less common and a major cause of syncope and sudden cardiac arrest in patients with HCM. The incidence of atrial fibrillation is ~2–3% per year and ~25% of patients with HCM develop atrial fibrillation during the course of the disease.[27–30] Atrial fibrillation with rapid ventricular rate is poorly tolerated in patients with HCM due to loss of atrial kick and diastolic dysfunction.[27,30,31] Factors associated with increased risk of cardiac arrhythmias in HCM include cardiac hypertrophy, myocardial fibrosis, LVOT obstruction, and left atrial size, the latter for atrial fibrillation.[29]

3.3 Dilated cardiomyopathy

DCM comprises a heterogeneous group of myocardial diseases characterized by LV dilatation and dysfunction.[6] DCM caused by mutations in the *LMNA* gene is a prototypic form of DCM that exhibits a high incidence of conduction defect and cardiac arrhythmias.[32] Conduction defects, such as atrioventricular block, sinus node dysfunction, and atrial fibrillation are common and often the early manifestations of DCM, leading to placement of a pacemaker in approximately one-third of the patients.[32] Likewise, ventricular arrhythmias develop in the majority of patients and are responsible for SCD in about half of the DCM patients with mutations in the *LMNA* gene.[32–34] DCM caused by truncating mutations in the *TTN* gene, encoding titin protein, is also associated with an increased incidence of ventricular arrhythmias, although this has not been consistently observed.[35,36]

A subset of DCM has been associated with pathogenic variants in the *SCN5A* gene, which encodes sodium voltage-gated channel alpha subunit 5 (SCN5A), commonly known as $Na_v1.5$, responsible for the fast depolarization phase (Phase 0) of the action potential in cardiac myocytes.[37] Mutations in the *SCN5A* gene are associated with a high burden of atrial and ventricular arrhythmias, cardiac conduction disease, and risk of SCD.[37–39] While mechanisms underlying different electrical phenotypes have been extensively studied using *in vitro* and *in vivo* approaches, little is known about whether and how sodium channel malfunction leads to ventricular dysfunction and dilation.[38]

4. Possible shared genetic basis of cardiac arrhythmia and hereditary cardiomyopathies

Shared genetic aetiology has been described for cardiomyopathies, particularly DCM and cardiac arrhythmias. Several genes implicated in cardiomyopathies and arrhythmias are discussed in this section.

4.1 *SCN5A*

The gene codes for SCN5A protein (also known as $Na_v1.5$), which is predominantly expressed in cardiac myocytes and localizes to plasma membrane at the IDs. It forms a voltage-sensitive channel that undergoes conformational changes in response to a shift in transmembrane voltage. The pore opens in response to rising transmembrane voltage in the early

phase of the action potential, enabling influx of sodium per electrochemical gradient. The consequent rise in the transmembrane potential results in closure of the pore, which is then followed by activation of NCX1 to normalize intracellular Na^+ concentration. Thus, this channel is responsible for Phase 0 of the action potential.[40]

Mutations in *SCN5A* are major causes of inherited arrhythmia syndromes. Gain-of-function (GoF) mutations in *SCN5A* cause long QT syndrome type 3 whereas loss-of-function (LoF) mutations are major causes of Brugada syndrome.[39,41] *SCN5A* mutations are also associated with atrial fibrillation, atrial standstill, cardiac conduction defects, sick sinus syndrome, idiopathic ventricular fibrillation, and multifocal ectopic Purkinje-related premature contractions.[41–46]

An arrhythmogenic phenotype as a consequence of *SCN5A* mutations is in accord with the known biological functions of the sodium channel in the generation of the action potential. However, unexpectedly, *SCN5A* mutations are also associated with DCM.[42,47] *SCN5A* mutations have been identified in ~1.7% of families with DCM.[48] Despite the existing data from several independent studies implicating *SCN5A* variants as causes of DCM, the causality of the *SCN5A* variants in DCM remains unsettled for various reasons. First, robust genetic evidence, such as co-segregation data in large DCM families, is lacking. Second, studies performed before the era of large-scale DNA sequencing were not designed to exclude the presence of concomitant pathogenic variants in other genes that might cause or contribute to the DCM phenotype. Thirdly, earlier studies included a rather small number of a control population, and therefore, any uncommon or rare variant identified in the cases was considered pathogenic. Fourth, the phenotype of DCM associated with the *SCN5A* mutations is typically reported in conjunction with conduction defects, supraventricular and ventricular arrhythmias, raising the possibility that the *SCN5A* variants were the susceptibility pathogenic variants for the arrhythmic phenotype and an undetected variant in another gene was responsible for DCM. Finally, both GoF and LoF *SCN5A* variants have been associated with DCM, rendering mechanistic explanation challenging.[49] Thus, despite the existing data suggesting *SCN5A* variants as the pathogenic variants in DCM, likely with low penetrance, it is plausible that *SCN5A* pathogenic variants predispose to cardiac arrhythmias and/or conduction defects in patients with DCM but are not the direct causes of DCM.

4.2 *LMNA*

A characteristic phenotypic feature of *LMNA* mutations is cardiac conduction defects, supraventricular and ventricular arrhythmias.[8,32] Electric abnormalities typically occur in the background of DCM but could occur in isolation and often as the initial manifestations of laminopathies, which comprise a group of distinct phenotypes associated with the *LMNA* mutations.[32,50,51] In a subset of laminopathies, neuromuscular involvement precedes cardiac manifestations by a decade.[52]

LMNA is a ubiquitously expressed nuclear envelope protein that interacts with chromatin through lamin-associated domains (LADs) to regulate gene expression.[53–55] In human cardiac myocytes, LMNA interacts with ~20% of the genome and affects expression of several thousand genes.[56] LADs have suppressive effects on gene expression, partly through increased CpG methylation and partly through recruitment of suppressive epigenetic markers.[56] Consequently, mutations in the *LMNA* gene, by shifting LADs to different genomic regions, could suppress expression of genes involved in cardiac arrhythmias, such as *SCN5A*.[57] Consequently, phenotypic pleiotropy of *LMNA* mutations is rather expected, even though specific mechanisms involved have yet to be delineated. Molecular basis of cardiac conduction defects and arrhythmias in DCM associated with the *LMNA* mutation is not known, suffice it to state that apoptosis is implicated in mice heterozygous for the *Lmna* gene.[58]

4.3 *TTN*

Mutations in the *TTN* gene are major causes of DCM and responsible for 15–20% of the DCM cases.[7,59,60] Because of its enormous size, the *TTN* gene carries a very large number of variants, including truncating variants (*TTN*tv), and multiple isoforms in the general population.[61] Genetic complexity of the *TTN* gene poses significant challenges in identification of the pathogenic variants. Despite such complexity, *TTN*tv have been associated with increased risk of ventricular arrhythmias and atrial fibrillation in patients with DCM.[35,62,63] In addition, *TTN*tv as well as LoF *TTN* variants have been associated with early-onset familial atrial fibrillation.[64,65] Similarly, genome-wide association studies have linked *TTN* gene variants with atrial fibrillation.[66] Along with these findings, rare coding *TTN* variants are associated with prolongation of the QT interval in the general population.[67] Furthermore, in the context of DCM, the association of *TTN*tv with cardiac arrhythmias seems to be independent of cardiac function.[62,63,68] Collectively, the existing data suggest a pro-arrhythmic effect of the pathogenic variants in the *TTN* gene, particularly in susceptibility to atrial fibrillation. The mechanism(s) responsible for susceptibility to cardiac arrhythmias, independent of structural remodelling, is unknown.

4.4 *FLNC*

Filamin C (FLNC) protein is a striated muscle-specific member of a family of actin-binding proteins. FLNC along with filamin A and filamin B are involved in multiple cellular processes, including cross-linking of cytoskeletal actin, mechano-transduction, and mechanical stability of sarcomeres, the latter through linking Z disc proteins to the dystrophin-associated-glycoprotein complex and integrins at the cytoplasmic cell membrane.[69,70]

Pathogenic variants in the *FLNC* gene were first shown to cause myofibrillar myopathy.[71] Although cardiac involvement in myofibrillar myopathy is not uncommon, the first direct evidence linking *FLNC* mutations to cardiomyopathies emerged through identification of missense mutations in multiple small families with HCM and detection of protein aggregation in the heart.[72] *FLNC* mutations also have been linked to RCM, DCM, and ACM.[73,74] The existing data suggest a high burden of cardiac arrhythmias in cardiomyopathies associated with the *FLNC* mutations.[75] In addition, a deletion mutation in the *FLNC* gene has been associated with familial ventricular arrhythmias and SCD in a sibling with normal cardiac function.[76] The mechanisms underlying predisposition to cardiac arrhythmias with the *FLNC* mutations remain unknown and expected to be complex given the diversity of its biological functions. Abnormal trafficking of ion channel proteins is an unexplored proposed mechanism of cardiac arrhythmias observed in cardiomyopathies associated with *FLNC* mutations.[77]

4.5 *RYR2*

The ryanodine receptor 2 (RYR2), encoded by the *RYR2* gene, localizes to sarcoplasmic reticulum (SR) and plays an essential role in excitation and contraction coupling in cardiac myocytes.[78] During the plateau phase of the action potential, Ca^{2+} enters the cell via the L-type voltage-dependent calcium channel CACNA1C (Cav1.2), which is located on the transverse tubules. Increased intracellular calcium triggers opening of the RYR2 channels and release of calcium from SR, a process that is referred to as Ca^{2+}-induced-Ca^{2+} release (CICR). The released calcium binds to troponin C, which induces conformational changes in the

troponin complex resulting in shifting the inhibitory arm of troponin I away from the acto-myosin complex. The process leads to flexion of the global head of the myosin over thin actin filament, resulting in displacement of the actin filament by the myosin head and muscle contraction. Excess intracellular calcium is then pumped back from the cytosol into SR by SR Ca^{2+} ATPase 2 (SERCA2) encoded by *ATP2A2* and pumped out of the cell by cell membrane NCX1, re-establishing the homoeostasis.[79]

Mutations in the *RYR2* gene are implicated in cardiac arrhythmias as well as cardiomyopathies, in accord with the prominent role of RYR2 in the intracellular Ca^{2+} release and the fundamental role of Ca^{2+} in regulating cardiac contraction and arrhythmogenesis.[80–83] Specifically, *RYR2* mutations are established causes of familial catecholaminergic polymorphic ventricular tachycardia (CPVT).[80,81] Pathogenic variants in the *RYR2* gene also have been reported in patients with cardiomyopathies, including ACM and LVNC.[82,83] As typical to all RYR2-mediated phenotypes, pathogenic variants in the *RYR2* gene confer increased risk of cardiac arrhythmias prior to and in the absence of measurable structural cardiac phenotype. A large genomic rearrangement in the *RYR2* gene that leads to loss of exon 3 has been associated with a compound phenotype of sinoatrial node and atrioventricular node dysfunction, atrial fibrillation, atrial standstill, and DCM.[84] Deletion and pathogenic variants involving exon 3 have been associated with exercise or stress-induced VT tachycardia as well as LVNC in independent probands and families, supporting the role of this gene not only in arrhythmogenesis but also in LV compaction during embryonic development.[85–87] The pathogenic role of *RYR2* variants in CPVT is well established, however, their role as causes of cardiomyopathies, perhaps with the exception of LVNC, is less certain. In accord with this notion, knock-in mouse models of *RYR2* pathogenic variants identified in CPVT or ACM patients do not exhibit structural remodelling reminiscent of ACM.[88,89] In addition to the genetic variants, various functional alterations in RYR2 channels have been identified as contributing to cardiac arrhythmias and dysfunction, as discussed later.

4.6 *JPH2*

Junctophilin-2 (JPH2) is predominantly expressed in the heart and acts as a structural protein within the junctional membrane complex that physically approximates the plasmalemmal L-type Ca^{2+} channel and RYR2 on the SR (reviewed in Ref.90). Rare variants in the *JPH2* gene have been identified in patients with HCM and have been shown to impart functional effects, such as cardiac hypertrophy and atrial fibrillation in *in vitro* and *in vivo* studies.[91–94] Likewise, a homozygous deletion variant in the *JPH2* gene has been reported in a patient with autosomal-recessive DCM.[95] A proposed mechanism pertains to impaired interaction of the mutant JPH2 with RYR2 proteins and consequent destabilization of Ca^{2+} release from the SR.[93]

4.7 *PLN*

PLN codes for a homopentameric protein phospholamban (PLN), which regulates cardiac contractility/relaxation by targeting ATP2A2 (SERCA2) in cardiac SR. Unphosphorylated PLN inhibits SERCA2, where its phosphorylation by protein kinase A (PKA) in response to cAMP of the adrenergic system releases it from SERCA2. The release removes the inhibitory effect of PLN on SERCA2, thereby facilitating removal of Ca^{2+} from the cytosol to SR and enhanced cardiac relaxation or lusitropy, as observed upon stimulation of the heart with catecholamines.

Mutations in the *PLN* gene cause DCM and ACM.[96–98] The phenotype is characterized by refractory heart failure and a relatively high prevalence of ventricular arrhythmias.[96–99] The molecular basis of cardiac arrhythmias in cardiomyopathies associated with the *PLN* mutations is largely unknown. Given the major role of PLN protein in regulating intracellular calcium concentration through inhibition of ATP2A2, mutations in the *PLN* gene are expected to predispose to cardiac arrhythmias through affecting calcium cycling in cardiac myocytes as in other forms of heart failure.[100]

4.8 *PKP2*

Plakophilin 2 (PKP2) is a desmosome protein located predominantly in the IDs and involved in mechano-sensing and stabilization of other ID proteins, including SCN5A and GJA1 (gap junction protein alpha 1 or connexin 43). Mutations in the *PKP2* gene are the most common causes of ACM.[101] Among genes coding for the desmosome proteins, only the *PKP2* gene has been associated with cardiac arrhythmias, independent of cardiomyopathy, albeit the data are not compelling.[102,103] Given co-localization of PKP2, SCN5A, and GJA1 proteins to the IDs, it is plausible that *PKP2* mutations de-stabilize localization and function of its binding partners and hence, predispose to cardiac arrhythmias, partially independent of cardiac contractile function.[19,104,105] Experimental data in murine models suggest that PKP2 deficiency leads to reduced transcript levels of genes involved in intracellular calcium handling/cycling, thereby disrupting intracellular calcium homoeostasis with a consequent increase in arrhythmogenesis.[106]

4.9 *RBM20*

Ribonucleic acid-binding motif protein 20 (RBM20) is a pre mRNA splicing factor that is highly expressed in striated muscle, in particular, cardiac muscle and regulates splicing of cardiac genes.[10] Pathogenic variants in *RBM20* are associated with DCM and ACM.[107–109] RBM20 alters splicing of several genes in cardiac myocytes, in particular, *TTN* and *RYR2*, which have been associated with cardiomyopathies as well as cardiac arrhythmias.[10,109] Differential splicing of calcium-handling genes *CACNA1C* and *CAMK2D* have been observed in iPSC-derived cardiac myocytes from patients with RBM20-associated DCM.[110] Data in the *Rbm20* knock-out mice indicate aberrant splicing of *Ryr2* and *Camk2d* genes resulting in increased intracellular Ca^{2+} overload as a mechanism for the pathogenesis of ventricular arrhythmias.[109] The findings suggest that treatment with an L-type Ca^{2+} channel blocker might reduce ventricular arrythmias in this particular form of cardiomyopathy.[109]

4.10 *HCN4*

Hyperpolarization and cyclic nucleotide 4 channel (HCN4) encoded by the *HCN4* gene, transports positively charged ions to cardiac cells (*Figure* 2). It is expressed mainly in the sinoatrial node in the adult heart but during murine embryonic development it is also detectable at a lower level in the trabecular (subendocardial) layer of myocardium.[111,112] The HCN4 channels play a crucial role in the automaticity of the sinus node through the generation of a slow diastolic depolarization during the Phase 4 of the cardiac action potential in response to increased intracellular cAMP concentration.[113] Expression level of *Hcn4* gene is downregulated in response to exercise training in mice, which may account for training-induced bradycardia.[114] Mutations in the *HCN4* gene are associated with sinus node dysfunction, sick sinus syndrome, and inappropriate sinus tachycardia, as well as exercise-induced ventricular ectopic beats.[115,116] In addition, *HCN4* mutations have been linked to LVNC and susceptibility to ventricular fibrillation occurring in conjunction with sinus bradycardia.[117,118] The putative mechanism(s) of LVNC

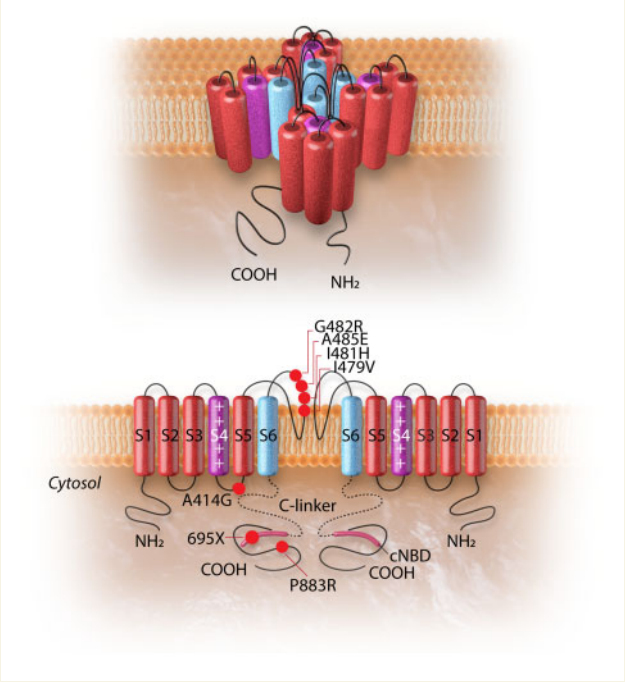

Figure 2 The HCN4 channel and the topology of the *HCN4* mutations associated with left ventricular non-compaction cardiomyopathy. The upper panel shows the 3D conformational structure of the HCN4 channel. The lower panel shows the liner structure of the HCN4 channel (two out of four subunits are shown). Each alpha-subunit is composed of six transmembrane helixes (S1–S6), a pore-forming loop, and intracellular N- and C-termini. The positively charged S4 helix (shown in purple) is the voltage sensor of the channel. The four S6 segments (shown in blue) of four-channel monomers together form the ion-conducting passage of the HCN4 channel. The C-terminus comprises of the C-linker (dotted line) and the cyclic nucleotide-binding domain (cNBD), which is connected to the channel core and mediates cyclic AMP-dependent changes in HCN channel gating. cAMP binding causes a conformation change that leads to the assembly of an active tetramer and channel opening. Red dots on the alpha-subunit shown on left indicate the sites of mutation associated with left ventricular non-compaction. The dot with a black dash indicates a truncation resulting from an insertion mutation leading to premature truncation of the protein at amino acid 695.

caused by the *HCN4* mutations relates to expression of this gene in the early cardiac progenitor cells that give rise to both compact and trabecular layers of the left ventricle as well as its role in normal compaction of the human foetal ventricles.[111,112]

4.11 *PRKAG2*

The gene codes for gamma 2 subunit of AMP-activate protein kinase, which sustains metabolism through regulating intracellular ATP concentration.[119] Mutations in the *PRKAG2* gene lead to glycogen storage in the heart mimicking HCM and Wolff–Parkinson–White syndrome, atrial fibrillation, and progressive infra-His conduction defect.[120–122] Pathological examinations of affected human hearts show vacuoles containing amylopectin, a glycogen-related substance.[123] Unlike the classic Wolff–Parkinson–White syndrome, the pre-excitation phenotype and cardiac arrhythmias in these patients likely result from structural disruption of annulus fibrosus by excess glycogen-laden cells. Experimental data suggest that PRKAG2 regulates voltage-gated sodium channels in rat ventricular myocytes, leading to prolonging action potential duration and production of arrhythmogenic early after depolarizations (EAD).[124] However, data in genetically modified mouse models suggest that pre-excitation and arrhythmias are direct consequences of glycogen storage in cardiac myocytes.[125]

4.12 *ABCC9*

The encoded ATP-binding cassette subfamily C member 9 (aka sulfonylurea receptor subunit 2A or SUR2) protein is a regulatory subunit of ATP-sensitive K^+ channel. Mutations in the *ABCC9* gene are known to cause Cantu syndrome, a disease characterized by a number of developmental abnormalities and congenital heart disease.[126] *ABCC9* mutations also have been identified in patients with DCM and paroxysmal atrial fibrillation.[127,128] The causal role of *ABCC9* mutations in these phenotypes remain to be established.

4.13 Other genes

Rare variants in *CACNA1C* and *CALM2*, encoding the voltage-dependent L-type Ca^{2+} channel subunit α1C and calmodulin 2, respectively, have been reported in patients with cardiac arrhythmias and cardiomyopathies.[129,130] However, the evidence to support the pathogenic role of these variants in cardiomyopathies is not compelling.

5. Risk factors predisposing to cardiac arrhythmias in cardiomyopathies

5.1 Causal genes/mutations

Genotype–phenotype correlation studies in cardiomyopathies have been compounded by the small sample size of the studies as well as genetic and phenotypic heterogeneity of the disease, rendering firm conclusions challenging. Despite these limitations, specific phenotypic characteristics hint to the underlying causal gene(s) in cardiomyopathies. For example, conduction defects, including atrial, atrioventricular, and left bundle branch blocks, supraventricular tachycardia, and ventricular arrhythmias are often observed in patients with DCM caused by the *LMNA* mutations.[131,132] Such phenotypic features, however, are not specific to the *LMNA* mutations, as they are also observed in Anderson Fabry disease, amyloidosis, and mitochondrial defects, among others. Mutations in *TTN* and desmosome genes are associated with a high incidence of atrial and ventricular arrhythmias as well as poor prognosis as opposed to those in cytoskeletal protein genes.[33,35,62,64,65,68] However, there is considerable phenotypic variability, as truncating *TTN* mutations also have been associated with a relatively mild form of DCM.[36] Several genes are implicated in susceptibility to cardiomyopathies as well as arrhythmogenic syndromes, as discussed earlier under possible shared genetic aetiology. Finally, functional genetic variants in genes encoding protein constituents of ion channels might predispose to cardiac arrhythmias in patients with hereditary cardiomyopathies.

5.2 Biological sex

Patient's biological sex, partly through the effects of sex hormones on gene expression and partly because of the differences in external factors,

such as physical activity, between males and females, is an important determinant of phenotypic expression of various cardiovascular diseases, including cardiomyopathies and arrhythmias. Sex-dependent differences in the phenotypic expression of disease are not because of differences in the genetic aetiology of cardiomyopathies, as the vast majority of cardiomyopathies are autosomal and not sex-linked diseases. In general, phenotypic expression of cardiomyopathies seems to be more pronounced in male than female patients, albeit there is considerable variability among cardiomyopathies as well as inconsistent findings among different studies.[7,133–135] The inconsistencies in findings also seem to be relevant to sex-dependent predisposition to cardiac arrhythmias in patients with cardiomyopathies.[133,136–138] Overall, ventricular arrhythmias seem to be more common in male patients with cardiomyopathies and Brugada syndrome, whereas female preponderance is well documented in patients with long QT syndromes.[136,137,139,140] In the context of specific cardiomyopathy genes, ventricular arrhythmias seem to be more common in male patients who carry mutations in the *LMNA* or *RBM20* gene.[34,136,141]

5.3 Age

Association of cardiac arrhythmias with age in hereditary cardiomyopathy is influenced by the presence of concomitant conditions as well as age-dependent expression of other cardiac phenotypes, such as myocardial fibrosis, cardiac hypertrophy, and chamber dilatation, among others. In addition, a number of molecular and cellular changes occur with advancing age, such as cell death and inflammation, which affect susceptibility to cardiac arrhythmias in hereditary cardiomyopathies.

Certain cardiac arrhythmias, such as atrial fibrillation exhibit age-dependent penetrance, typically occurring in older age, whether in the context of cardiomyopathies or otherwise.[28] In contrast, ventricular arrhythmias in cardiomyopathies and certain channelopathies typically occur at a young age and are major causes of SCD in individuals <40 years of age.[142,143] A notable example is HCM, which is considered among the most common causes of SCD in the young.[142] In contrast, atrial fibrillation, which occurs in about a quarter of the HCM patients, typically presents late in the course of the disease.[28] Ventricular arrhythmias are often the first manifestations of ACM and might indicate disturbed ion channel functions in cardiac myocytes in the presence of desmosome mutations.[103,144,145] The early presentation of cardiac arrhythmias in ACM, that is cardiac arrhythmias manifesting in the absence of cardiac dysfunction, suggests a lower threshold for dysregulation of cardiac myocyte electric activity than mechanical function in the presence of mutations in the desmosome proteins. Alternatively, it is also possible that early cardiac arrhythmias originate from the non-myocyte cells in the heart that express the mutant desmosome proteins, such as the conduction system cells, as suggested by the experimental data.[146] Cardiac arrhythmias also occur late in the course of ACM and typically in the context of cardiac dysfunction, as in other forms of heart failure.

Cardiac arrhythmias in patients with DCM typically occur late and in the presence of cardiac dysfunction. However, DCM associated with *LMNA* mutations often exhibits early onset of cardiac conduction defects and supraventricular arrhythmias at a younger age, preceding the onset of cardiac dysfunction.[8] Likewise, ventricular arrhythmias occur at a relatively young age in patients with DCM associated with *PLN, FLNC,* and *RBM20* mutations.[74,98,108] Because of a relatively high prevalence of ventricular arrhythmias there is considerable phenotypic overlaps between DCM and ACM in patients with mutations in *PLN*, *FLNC*, and *RBM20* genes.

5.4 Ethnic background

The prevalence of the underlying causal mutations is not known to differ significantly among populations with different ethnic backgrounds, whereas phenotypic expression of cardiomyopathies could vary because of the modifier effects of the genetic backgrounds as well as environmental factors. Phenotypic expression of cardiac hypertrophy is more pronounced and the risk of heart failure is higher in African–American patients with HCM, as compared to Caucasians.[147] In contrast, the incidence of atrial fibrillation is lower among the African–American patients with HCM as compared to Caucasians and that of ventricular arrhythmias does not seem to be different.[147]

BAG3 mutations have been associated with worse clinical outcomes in African–American patients with DCM.[148] However, association of cardiac arrhythmias with ethnic background in patients with DCM caused by *BAG3* mutations remains unknown. Likewise, there are ethnic differences in the prevalence of ACM and SCD in patients with ACM.[11,149] Accordingly, ACM is more common in certain regions of Italy where it accounts for up to 20% of the cases of SCD in athletes.[149] It is unclear whether the differences are reflective of differences in the genetic backgrounds of the individuals or are secondary to factors that facilitate diagnosis of the disease.

5.5 Physical exercise

Observational studies suggest an association between sport activities and SCD, particularly in young patients with HCM.[4] However, a recent randomized prospective study showed that patients with HCM tolerate moderate-intensity exercise well without occurrence of significant arrhythmias.[150] Overall, the incidence of serious cardiac arrhythmias or SCD during physical exercise seems to be relatively low, suggesting that exercise may not be a major risk factor for induction of serious ventricular arrhythmias or SCD in HCM.[151]

Physical exercise is considered a risk factor for cardiac arrhythmias in ACM, a disease caused primarily by mutations in genes encoding desmosome proteins.[152–154] In the context of specific mutations, intense exercise in patients with the *TMEM43* p. Ser358Leu mutation is associated with a marked increase in the number of appropriate defibrillator shock, which is a surrogate indicator of malignant ventricular arrhythmias.[154] Multiple mechanisms are likely to be involved in the pathogenesis of exercise-induced cardiac arrhythmias in cardiomyopathies. For example, physical exercise by provoking the adrenergic system could activate cAMP-dependent PKA and subsequent phosphorylation of ion channels, affecting their function and leading to arrhythmias during exercise.[155–157] Likewise, exercise could induce cardiac arrhythmias by activating the stretch responsive ion channels. Moreover, exercise could alter interaction of the desmosome proteins with a subset of ion channels, such as SCN5A (Nav1.5) that located at the IDs.[158] Chronic exercise could affect susceptibility to cardiac arrhythmias by inducing molecular and structural remodelling in the heart. In keeping with the beneficial effects of exercise in other cardiovascular diseases, a recent study in a mouse model suggested beneficial effects of exercise in reversal of dysregulated transcriptional pathways in ACM.[159]

5.6 Other susceptibility factors

Molecular and cellular inflammatory responses are observed in the myocardium of patients with ACM.[160] The inflammatory response is likely due to internal factors but could also be triggered by external factors, such as viruses. Cardiotropic viruses have been detected in the myocardium of patients with ACM.[161] It is unclear whether viruses contribute to the pathogenesis of cardiac arrhythmias in ACM, although proteolytic cleavage of dystrophin by coxsackieviruses has been reported to lead to cardiac dilatation and dysfunction.[162]

Although the presence of concomitant CAD and myocardial ischaemia in patients with HCM is associated with adverse outcomes, its role in predisposition to cardiac arrhythmias is unclear.[163] Finally, presence of LV systolic dysfunction, represented as elevated plasma levels of biomarkers of cardiac dysfunction, increases the risk of cardiac arrhythmias in patients with cardiomyopathies, as in other forms of heart failure with reduced EF.[164,165]

6. Mechanisms of cardiac arrhythmias in hereditary cardiomyopathies

The underpinning mechanisms of cardiac arrhythmias in hereditary cardiomyopathies are not distinct from those involved in primary arrhythmia syndromes, suffice it to state that the arrhythmogenic substrates differ. Mechanisms of cardiac arrhythmias in primary arrhythmia disorders have been covered in other articles in the Spotlight issue. Therefore, the mechanisms are only briefly mentioned.

Re-entrant circuits and abnormal impulse formation can both contribute to arrhythmias.[166,167] Re-entrant arrhythmias are more likely to occur in the presence of extensive fibrosis, which contributes to heterogeneous conduction with slow or discontinuous electrical propagation. This may serve as a substrate for re-entrant ventricular arrhythmias that can originate during normal sinus rhythm.[168] In addition to fibrosis, downregulation of connexins may contribute to conduction delays, increased heterogeneity in impulse propagation, and an increased dispersion of action potential durations.[169]

Abnormal impulse formation represents the second major arrhythmia mechanism associated with cardiomyopathies, and can be caused by enhanced automaticity or triggered activity. Enhanced automaticity is the result of diastolic depolarizations due to net inward current during Phase 4 of the action potential. Abnormal automaticity is enhanced by β-adrenergic stimulation, which is consistent with clinical studies in patients with HCM showing that greater than half of all ventricular arrhythmias were associated with moderate to intense physical activity.[170] In addition, triggered activity can result from depolarizations that occur during or following cardiac action potentials (APs). EADs occur during Phase 2 or 3 of the AP, whereas delayed afterdepolarizations (DADs) occur after repolarization has been completed. When the amplitude of an EAD or DAD research membrane threshold potential, a spontaneous action potential referred to as triggered activity can occur.[167] The development of EADs often depends on the reduced availability of repolarizing K^+ current.[171] DADs on the other hand are mostly observed under conditions that augment intracellular Ca^{2+} release and increased sympathetic activity, as seen in hypertrophied and failing hearts.[172] Interestingly, frequent ventricular premature depolarizations have been associated with cardiomyopathy adding more complexity to our understanding of arrhythmias associated with cardiomyopathy.[173]

7. Pathogenesis of cardiac arrhythmias in hereditary cardiomyopathies

The major components involved in the pathogenesis of cardiac arrhythmias in hereditary cardiomyopathy entail two intertwined components of ion channel abnormalities and pro-arrhythmic structural remodelling, which are discussed.

7.1 Pro-arrhythmic structural remodelling in cardiomyopathies

Whereas early cardiac arrhythmias in hereditary cardiomyopathies are typically due to changes in ion channel functions, as discussed earlier, late arrhythmias are generally associated with structural remodelling of the cardiac chambers.

7.1.1 Cardiac hypertrophy

Severe cardiac hypertrophy is considered a risk factor for cardiac arrhythmias and SCD in patients with HCM.[26,174] Cardiac hypertrophy affects myocardial electric properties, such as voltage amplitude and conduction, producing an arrhythmogenic substrate.[175] At the molecular level, increased cytosolic Ca^{2+} resulting from increased Ca^{2+} entry through the L-type calcium channels and reduced exchange through NCX1 could lead to DADs. The latter is implicated as a mechanism of cardiac arrhythmias in cardiac hypertrophy associated with HCM.[176]

7.1.2 Cardiac dilatation

Progressive cardiac dilatation and remodelling in cardiomyopathies is commonly associated with complex electric remodelling in the heart, involving K^+, Na^+, and Ca^{2+} currents, as well as NCX electric properties, which collectively lead to altered spatiotemporal gradient of repolarization, prolongation of the action potential duration (APD), and increased excitability of atrial and ventricular myocytes (reviewed in Ref.[177]). Molecular changes, which are mainly documented in heart failure with reduced EF and in model organisms but largely are expected to pertain to human DCM as well. Specifically, transcript levels of several genes coding for the components of Na^+, K^+, and Ca^{2+} channels are reduced in the endomyocardial biopsy samples from patients with DCM and in model organisms.[178–180] In addition, cardiac dilatation and failure is associated with activation of a number of kinases such as PKA and CAMK2, which target ion channel proteins for phosphorylation and affect their functional properties.[181,182]

Loss of inactivation of SCN5A (Nav1.5) channels leads to increased late inward Na^+ current, whereas K^+ currents, including I_{to}, are downregulated, and Ca^{2+} currents are upregulated in dilated hearts.[183–186] The net result of these alterations is the prolongation of the APD. Additionally, Calcium calmodulin-dependent protein kinase II (CAMK2)-mediated phosphorylation of RYR2 in the failing hearts leads to calcium leak from the SR in the setting of downregulated ATP2A2 protein levels and reduced Ca^{2+}-uptake into the SR.[187,188] In addition to ion channels and calcium-handling proteins, disorganization of GJA1 (Cx43), a protein critical for the normal impulse conduction in the heart, can contribute to the arrhythmogenicity of failing hearts.[189]

7.1.3 Myocardial fibrosis

Data on the association of myocardial disarray and fibrosis with cardiac arrhythmias in HCM are suggestive but not conclusive. Myocardial

fibrosis, assessed by late gadolinium enhancement (LGE), as a surrogate marker, has been shown to be a modest risk factor for SCD, and hence, by inference cardiac arrhythmias.[190–192] While some studies suggest the extent of LGE correlates with the risk of SCD in HCM, others suggest the simple detection of LGE is a risk factor for SCD.[190–192]

7.1.4 Myocyte disarray

Myocardial disarray, as assessed by diffusion tensor, cardiac magnetic resonance imaging has been associated with an increased risk of ventricular arrhythmias in HCM.[193] Experimentally myocardial disarray has been linked to altered transmural distribution of connexin 43, providing a substrate for cardiac arrhythmias in HCM.[194]

7.2 Functional defects in ion channels in cardiomyopathies

An exquisite ionic homoeostasis is maintained by a large set of molecules in cardiac myocytes to orchestrate orderly cycles of excitation and contraction throughout life (*Figure 3*). Consequently, a large array of disturbances, whether genetic or otherwise, could disrupt various components of this delicate balance and lead to dysregulation of excitation-contraction cycles, affecting both cardiac rhythm as well as mechanical function. In addition to genetic mutations, which could directly affect structure and function of the ion channels and therefore, contribute to cardiac arrhythmias (as discussed in this spotlight issue), a number of secondary changes, resulting from impaired cardiac function or altered signalling pathways could also affect ion channel function and contribute to arrhythmogenesis in cardiomyopathies. Some of the secondary changes in ion channels, occurring in the context of hereditary cardiomyopathies, are discussed.

7.2.1 Functional defects in cardiac sodium current

The mechanisms underlying SCN5A-mediated cardiac arrhythmias in DCM patients are not known. It is plausible that *SCN5A* LoF variants promote arrhythmias through slowing the conduction and initiating a re-entry, whereas GoF mutations induce triggered activity during the repolarization or diastolic phase of cardiac cycle.[39,41] Whereas the mechanisms responsible for Long QT and Brugada syndromes or conduction defects caused by *SCN5A* mutations are partially understood, it is unclear whether similar or distinct mechanisms are also involved in the pathogenesis of cardiac arrhythmia occurring in the context of DCM in patients carrying pathogenic variants in the *SCN5A* gene.

As discussed earlier, it is unclear whether pathogenic variants in *SCN5A* cause DCM and if so, how they lead to cardiac dilatation and dysfunction. Several hypotheses have been proposed and discussed recently (*Figure 4*).[195] On one end of the spectrum, one may posit that DCM is a consequence of long-standing cardiac conduction abnormalities and arrhythmias resulting from SCN5A protein functional abnormalities, as in 'tachycardia-induced cardiomyopathy'.[195] This hypothesis is supported by the concomitant presence of cardiac conduction abnormalities and arrhythmias in the majority of DCM patients carrying pathogenic variants in the *SCN5A* gene.[47,48] On the opposite end of the spectrum, it is postulated that DCM is a direct consequence of SCN5A channel dysfunction, meaning that the structural phenotype is primarily driven by electrical abnormalities. Accordingly, increased Na^+ influx into cardiac myocyte caused by *SCN5A* GoF mutations could lead to compensatory activation of the NCX1 or the Na^+/H^+ exchanger, resulting in intracellular Ca^{2+} overload or acidification, respectively, and consequent impaired excitation–contraction coupling.[196–198] A third hypothesis implicates impaired subcellular localization and interaction of SCN5A with other structural proteins, such as PKP2, DSG2, dystrophin, Lim domain binding 3, and caveolin 3, as the putative mechanism for DCM (reviewed in Ref.[199]). Several other putative mechanisms are also considered, including presence of concomitant pathogenic variants in other genes being responsible for DCM, effects of mutations on dimerization and post-translational modifications of SCN5A, such as phosphorylation, acetylation, ubiquitination, and nitrosylation; as well as disruption of SCN5A trafficking and function (reviewed in Ref.[200]).[201–205] Given the heterogeneity of the *SCN5A* mutations associated with DCM, one could envisage multiple mechanisms contributing to the pathogenesis of cardiac dilatation and dysfunction.

The interplay between SCN5A and DCM is further compounded by the effects of heart failure on SCN5A functions.[206] Reduced peak Na^+ current and prolongation of APD in cardiac myocytes are observed in heart failure models.[207–210] Likewise, increased late Na^+ current (I_{NaL}) during the plateau phase of action potential resulting from impaired inactivation of the channel is implicated in the prolongation of action potential and arrhythmogenesis.[183] The putative underpinning mechanisms responsible for altered Na^+ current are reduced level of SCN5A protein, disrupted subcellular localization, deficient glycosylation of SCN5A, and altered phosphorylation of SCN5A.[183,207,209,211,212] Moreover, epigenetic suppression of *SCN5A* gene expression is implicated in reduced peak I_{Na} in an iPSC-cardiomyocyte model of DCM associated with an *LMNA* mutation.[57] Furthermore, reduced levels of full-length *SCN5A* transcript due to aberrant splicing have been observed in the myocardium of patients with HCM caused by the *MYPBC3* mutations.[213] Moreover, increased I_{NaL} has been implicated in the pathogenesis of HCM.[214] However, a clinical trial with ranolazine in humans, an inhibitor of I_{NaL}, did not show significant effect on exercise performance, indices of diastolic function, NT-proBNP levels, or quality of life, casting doubt about the pathogenic role of this current in HCM.[215] Finally, *PKP2* LoF variants are associated with decreased I_{Na} density and voltage-dependent inactivation properties of SCN5A, providing a potential mechanism for arrhythmogenesis in ACM.[103,216] Mechanistically, reduced peak I_{Na} current increases the susceptibility to re-entry by slowing impulse conduction. Increased I_{NaL} because of slower rate of inactivation antagonizes repolarization, causes APD prolongation, and increases susceptibility to EADs, mechanisms similar to those observed in long QT syndrome type 3. Thus, in cardiomyopathies, structural and functional modification of SCN5A secondary to cardiac dysfunction could be responsible for cardiac arrhythmias.

7.2.2 Functional defects in cardiac calcium current

Cardiac contraction and relaxation are regulated by a delicate set of channels and pumps that enable balanced influx and efflux of calcium during a cardiac cycle. Voltage-dependent L-type Ca^{2+} channels are activated during depolarization phase of the action potential to enable influx of Ca^{2+} into the cytosol. The latter triggers CICR through the RYR2 from the SR, which initiates acto-myosin contraction. This is followed by efflux of Ca^{2+} from the cytosol, which is carried out by the NCX1 as well as sequestration of Ca^{2+} back into the SR by the ATP2A2 (SERCA2a) pump, mediating dissociation of actin and myosin and muscle relaxation.[79]

The role of genetic variants in the components of Ca^{2+} cycling in cardiac muscle in susceptibility to cardiac arrhythmias in cardiomyopathies was discussed earlier. Secondary changes in the component of Ca^{2+} handling channels and transporters are also implicated in arrhythmogenesis

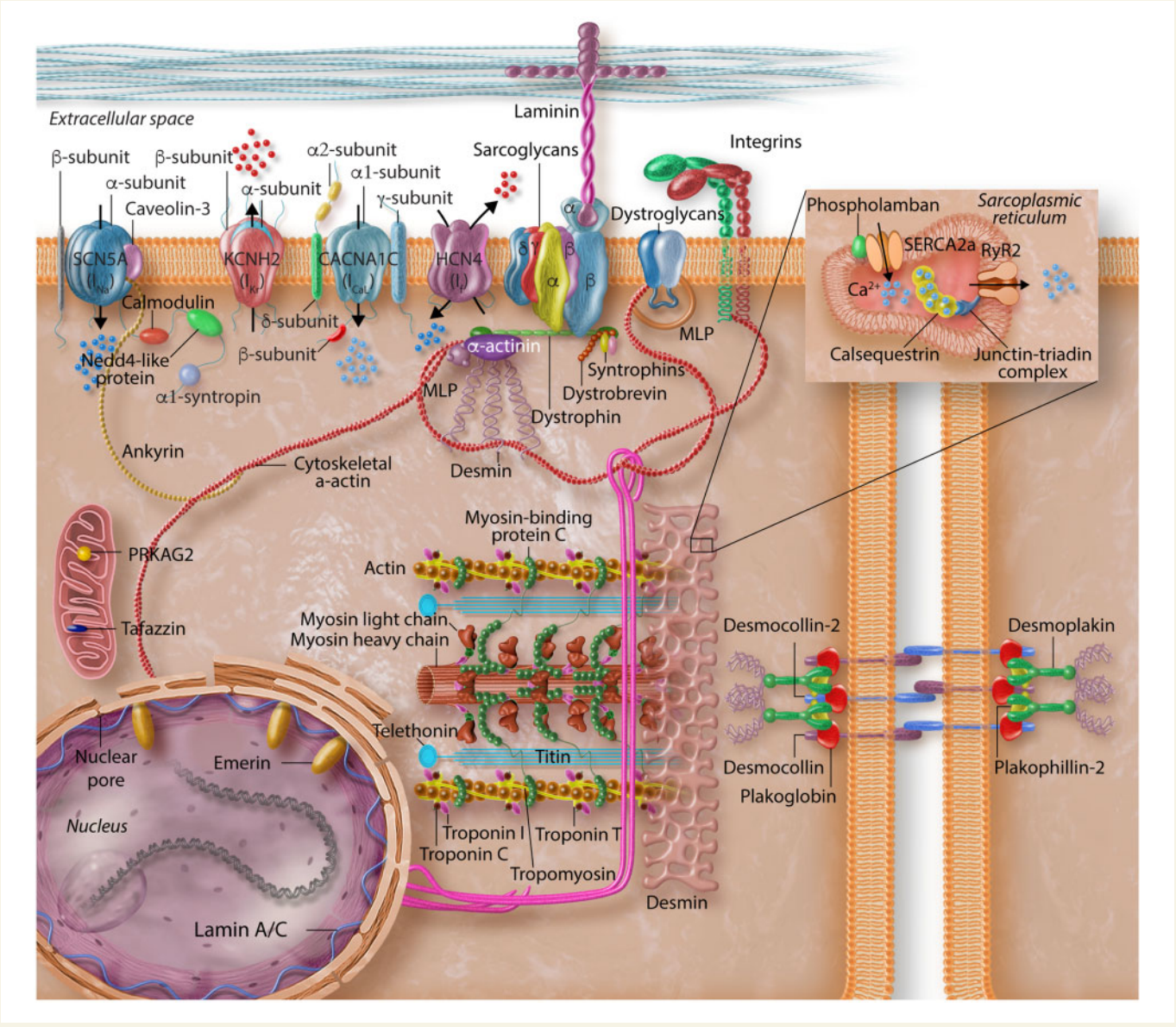

Figure 3 Schematic representation of the structural elements of cardiomyocytes implicated in the pathogenesis of arrhythmias in inherited cardiomyopathies. Protein constituents of cardiac myocyte structural proteins and ion channels are depicted to reflect the complexity of the interactions that mediate maintenance of normal cyclic excitation and contraction cycles throughout life.

associated with inherited cardiomyopathies (reviewed in Refs[217,218]). Mouse models of cardiomyopathies exhibit altered function of the L type Ca^{2+} channels leading to excess intracellular Ca^{2+} load.[109,219] The components of the channels and pumps involved in maintaining Ca^{2+} homoeostasis, including the RYR2, are modified upon phosphorylation by various kinases and oxidative stress, which are often altered in cardiomyopathies[220,221] (reviewed in Ref.[222]).

CAMK2, a major calcium-handling protein, is activated and contributes to arrhythmogenesis in cardiomyopathies. Enhanced activation of results in increased phosphorylation of RYR2 and increased diastolic RYR2-mediated Ca^{2+} leak, which are implicated in arrhythmogenic Ca^{2+} waves and VT in the mdx mouse model of DCM.[223] Likewise, increased CAMK2 activity, hyper-phosphorylation of the RYR2, super inhibition of ATP2A2, and reduced Ca^{2+} transients are implicated as the mechanisms responsible for cardiac arrhythmias in DCM caused by the *PLN* mutations.[224] Moreover, increased production of reactive oxygen species, commonly observed in cardiomyopathies, promotes both CAMK2 activation and enhanced RYR2-mediated Ca^{2+} leak, promoting arrhythmogenesis.[225] Enhanced CAMK2 activity might induce pro-arrhythmic changes by targeting SCN5A upon phosphorylation, which could result in enhanced late depolarization current and prolongation of action potential duration.[226]

Cardiac myocytes isolated from human hearts of patients with HCM exhibit increased late Na^{+} current, increased L-type Ca^{2+} current, prolonged Ca^{2+} transients, and higher diastolic Ca^{2+} concentrations.[227] In accord with these observations, CAMK2 activity and enhanced CAMK2-

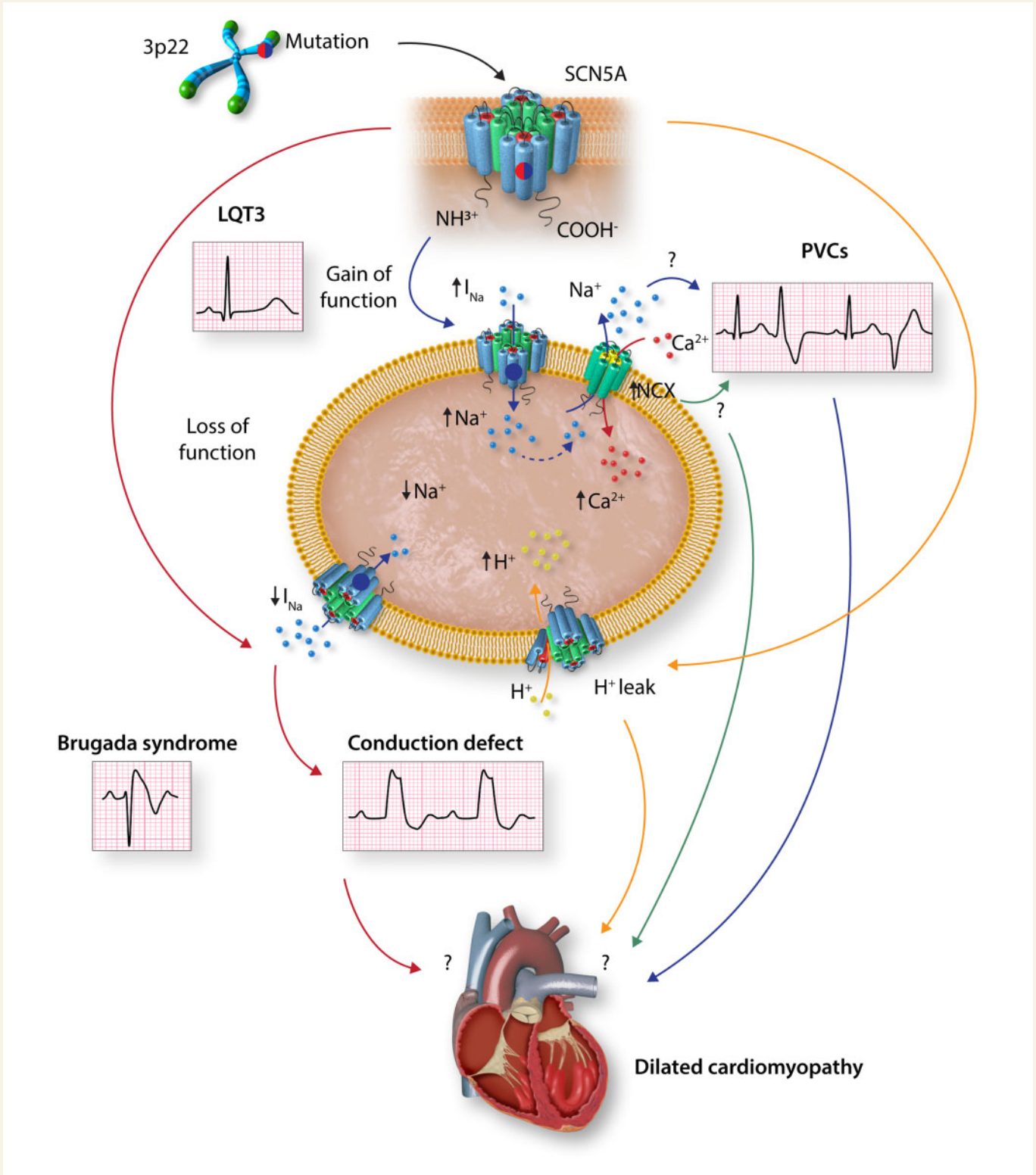

Figure 4 Graphic illustration of putative mechanisms underlying dilated cardiomyopathy associated with *SCN5A* mutations. Gain-of-function (GoF) *SCN5A* variants are known to cause long QT3 syndrome. GoF variants could also increase I_{Na} current and to frequent premature ventricular contractions or ventricular tachycardia, which might contribute to left ventricular dilatation and dysfunction. Likewise, GoF variants could induce compensatory activation of the Na^+/Ca^{2+} exchange protein, resulting in intracellular Ca^{2+} overload and consequently impaired excitation–contraction coupling and contractile dysfunction. Loss-of-function *SCN5A* variants are known to cause Brugada syndrome and cardiac conduction defects, the latter could lead to cardiac structural remodelling. *SCN5A* pathogenic variants could also result in proton leak into the cytosol, acidify the cytosol, and myocardial dysfunction. Experimental data to support these hypotheses are scant. I_{Na}, inward depolarizing sodium current; $Na_V1.5$, voltage-gated sodium channel α-subunit; NCX, Na^+/Ca^{2+} exchanger; PVC, premature ventricular contractions.

mediated phosphorylation of the RYR2 are implicated in an aberrant intracellular Ca^{2+} handling in a mouse model of HCM caused by a mutation in the *TNNT2* gene.[228]

PKP2, a major causal gene for ACM in humans, is implicated in regulating expression of several genes involved in Ca^{2+} homoeostasis, as deletion of *Pkp2* gene in mice is associated with downregulation of expression of *Ryr2*, *Ank2* (encoding ankyrin B), *Cacna1c*, *Trdn* (triadin), and *Casq2* (calsequestrin).[106] Downregulation of expression of these genes is associated with a number of changes in Ca^{2+} homoeostasis, leading to increase Ca^{2+} transient amplitude and duration, and early as well as delayed after transients.[106] The data are insufficient to conclude that the changes are reflective of transcriptional activity of the PKP2 protein.[229]

Expression level of JPH2, a key junctional membrane protein that is essential for proper intracellular Ca^{2+} handling in cardiomyocytes, is reduced in human heart biopsies obtained from patients with HCM.[230] Functionally, experimental downregulation of JPH2 using an RNA interference is associated with reduced Ca^{2+} transient, increased Ca^{2+} store, impaired cardiac contractility, and increased mortality in a cardiac-specific *Jph2* knockdown mice.[230] Whether these changes contribute to arrhythmogenesis in cardiomyopathies, while expected, remain to be shown.

Finally, auto-antibodies against the L-type Ca^{2+} channel have been identified in a subset of patients with DCM and their presence has shown to be and independent predictor of VT and SCD.[231,232] The findings are in accord with data showing that anti-Ro antibodies, which are linked to complete heart block in auto-immune diseases, inhibit L- and T-type calcium channels (reviewed in Ref.[233]). Observational data suggest prolongation of the QT interval and increased frequency of ventricular ectopic beats in patients with anti-Ro antibodies.[234] Likewise, *ex vivo* experimental data show that affinity-purified auto-antibodies prolong the APD and promote triggered activity due to early afterdepolarizations leading to VT.[231] Whereas the role of auto-antibodies in conduction defects, particularly congenital AV block, is well established, their role and the pertinent mechanisms in the pathogenesis of cardiac arrhythmias in human hereditary cardiomyopathies remain to be established.

7.2.3 Functional defects in cardiac K^+ current

Potassium channels are comprised of tetrameric transmembrane proteins that enable specific permeation of the K^+ ions, but not other ions, across the cytoplasmic membrane. The K^+ channel units are encoded by over two dozen genes in the genome, which are ubiquitously expressed in various cell types, including cardiac myocytes. The primary function of the K^+ in cardiac myocytes is to restore the membrane potential to its resting level, that is regulate repolarization (reviewed in Ref.[235]). The rapid and slow rectifier K^+ channels, referred to as I_{Kr} and I_{Ks}, regulate efflux of K^+ during Phase 3 of the action potential in ventricular cardiac myocytes and are the main determinants of the refractory period and therefore, the APD. In addition, the inward rectifier channels (I_{K1}), fast transient outward current (I_{tof}), and slow transient outward current (I_{tos}) contribute to efflux of K^+ during various phases of action potential. Genetic variants, transcriptional changes, and post-translational modifications of various proteins involved in the K^+ currents are expected to affect susceptibility to cardiac arrhythmias in patients with cardiomyopathies.

There are scant data on K^+ channel abnormalities in specific forms of genetic cardiomyopathies. A pathogenic LoF variant in *KCNQ1*, encoding a subunit of I_{Ks}, has been associated with reduced I_{Ks} current and VT in a patient with DCM.[236] In addition, auto-antibodies against KCNQ1 protein, also known as Kv7.1, have been detected in a subset of patients with DCM and shown to increase I_{Ks} current density and shorten the QT interval.[237]

In the setting of heart failure in patients with cardiomyopathies, the changes are expected to be largely similar to those observed in other forms of heart hypertrophy and failure. Notably, K^+ currents are reduced in the failing myocardium, resulting in slow repolarization and prolongation of the APD, setting a pro-arrhythmic substrate.[238–241] Likewise, ventricular myocytes isolated from patients with DCM show prolongation of the APD duration and slower repolarization phase.[242] At the current level, I_{Ks}, I_{K1}, and I_{to} are generally suppressed whereas small calcium-activated K^+ current is increased in heart failure (reviewed in Ref.[238]). The changes in the expression level of small calcium-activated K^+ current proteins have not been consistently observed.[243] In conjunction with suppressed K^+ currents and prolongation of APD, transcript levels of several genes encoding K^+ channel protein subunits are also reduced in cardiac myocytes isolated from experimental models of cardiomyopathies.[179,244] Moreover, changes in K^+ channels in iPSC-cardiomyocytes generated from patients with cardiomyopathies also have been reported, albeit the findings are preliminary.[245,246]

7.2.4 Functional defects in cardiac Cl^- current

Several chloride channels are expressed in the heart including, CFTR, ClC2, ClC3, CLCA, TMEM16A, and BEST1; and implicated in the regulation of both repolarization and depolarization (reviewed in Ref.[247]). Alterations in cardiac chloride channels have been implicated in cardiac arrhythmia, myocardial hypertrophy, and heart failure.[247] For example, swelling-sensitive Cl^- channel ($I_{Clswell}$) is activated in cardiac hypertrophy and failure and contributes to shortening of the APD, depolarization of the resting membrane potential, and induction of arrhythmias.[248]

7.3 Functional defects in cardiac connexins

Gap junctions are comprised of clusters of connexin proteins, which span the cytoplasmic membrane, form channels, and regulate cell-to-cell electrical and metabolic coupling (reviewed in Ref.[249]). Six connexin molecules assemble to form a connexon (hemichannel), which connects with the connexon of the neighbouring cardiac myocyte to form a gap junction in the IDs.[249] The human genome codes for 21 connexin proteins with similar structural topology.[250] Connexins show tissue and cell type-specific expression, enabling unique permeability and gating properties as well as ability to interact with regulatory partners in different tissues.[251] GJA1 (gap junction protein alpha 1 or Cx43) is the most abundantly expression connexin in cardiac myocytes, followed by GJA5 (gap junction protein alpha 5 or Cx40), and GJC1 (gap junction protein gamma 1 or Cx45).[249] In addition, GJB2 (gap junction protein beta 2 or Cx26) and GJD3 (gap junction protein delta 3 or Cx31.9) are also expressed in cardiac myocytes, albeit at low levels. GJA1 and GJA5 are predominantly expressed in ventricular (>90%) and atrial cardiac myocytes, respectively, and less in the cardiac conduction system, whereas GJC1 expression is found mainly in the cardiac conduction system.[249,252,253] Diversity in the expression levels and composition of cardiac connexins leads to homomeric and heteromeric constitution of connexons with variable biological properties. In addition, connexins undergo considerable remodelling in the heart during cardiac development and under pathological conditions, both in terms of expression levels as

well as post-translational modifications, including phosphorylation, which regulate its gating, trafficking, assembly/disassembly, distribution, and degradation.[254,255]

There is no compelling human molecular genetic data to link pathogenic variants in genes encoding cardiac connexin with cardiomyopathies and arrhythmias (reviewed in Ref.[256]). However, molecular remodelling of the IDs in cardiomyopathies is associated with reduced levels, post-translational modifications, and localization of connexins in the heart.[19,257–259] The changes are particularly notable for GJA1 (Cx43) in the advanced stages of ACM, wherein the total level and localization of GJA1 to IDs are markedly reduced.[19,257–259] However, altered expression and localization of GJA1 are not specific to ACM but are also observed in other forms of heart failure and in cardiomyopathies, including DCM, HCM, and model organisms of cardiomyopathies.[194,243,260–262]

The precise functional impacts of altered GJA1 expression and localization on susceptibility to cardiac arrhythmias are not well established. Conventionally, alterations in are thought to enhance susceptibility to cardiac arrhythmias by altering action potential conduction in the heart. However, part if not the whole effects of connexins might be mediated through their interactions with SCN5A and electrotonic/ephaptic conduction (reviewed in Ref.[263]).

Atrial fibrillation is associated with changes in the expression level and location of GJA5 (Cx40) in the atrial tissue and pulmonic veins (reviewed in Ref.[264]). However, in the context of cardiomyopathies, the role of GJA5 in susceptibility to atrial arrhythmias remains unclear.

8. Treatment

Conventional approaches, comprised of pharmacological therapy, radiofrequency ablation, and implantable cardioverter/defibrillator (ICD) implantation, are applied for the treatment of cardiac arrhythmias in patients with hereditary cardiomyopathies, and therefore, not discussed. Nevertheless, it merits noting that because of the presence of an arrhythmogenic substrate the threshold for implantation of an ICD in the management of cardiac arrhythmias is relatively low. The notion is partly reinforced by the success of radiofrequency ablation in reducing ventricular arrhythmias in patients with ACM and the effectiveness of ICDs in prevention of SCD in patients with HCM.[265–267]

9. Concluding remarks

Cardiac arrhythmias are common and dangerous manifestations of hereditary cardiomyopathies. ACM is the prototypic form of hereditary cardiomyopathies wherein ventricular arrhythmias are the cardinal and early manifestations of the disease, typically occurring prior to the onset of cardiac dysfunction. Numerous mechanisms are implicated in predisposition to cardiac arrhythmias in hereditary cardiomyopathies, including a shared genetic aetiology, pro-arrhythmic structural and molecular myocardial remodelling, altered mRNA splicing of genes regulating ion currents, post-translational modifications of ion channels, and trafficking of proteins involved in electric activity of the heart. Elucidation of the genetic and non-genetic basis of cardiac arrhythmias in hereditary cardiomyopathies might pave the way for identification of new drug targets and development of new therapies.

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