Emerging roles of junctophilin-2 in the heart and implications for cardiac diseases

David L. Beavers[1,2], **Andrew P. Landstrom**[1,3], **David Y. Chiang**[1,2], **and Xander H.T. Wehrens**[1,4,5]*

[1]Cardiovascular Research Institute, Baylor College of Medicine, Houston, TX, USA; [2]Translational Biology and Molecular Medicine Program, Baylor College of Medicine, Houston, TX, USA; [3]Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA; [4]Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, TX, USA; and [5]Deptartment of Medicine (Cardiology), Baylor College of Medicine, Houston, TX, USA

Cardiomyocytes rely on a highly specialized subcellular architecture to maintain normal cardiac function. In a little over a decade, junctophilin-2 (JPH2) has become recognized as a cardiac structural protein critical in forming junctional membrane complexes (JMCs), which are subcellular domains essential for excitation–contraction coupling within the heart. While initial studies described the structure of JPH2 and its role in anchoring junctional sarcoplasmic reticulum and transverse-tubule (T-tubule) membrane invaginations, recent research has an expanded role of JPH2 in JMC structure and function. For example, JPH2 is necessary for the development of postnatal T-tubule in mammals. It is also critical for the maintenance of the complex JMC architecture and stabilization of local ion channels in mature cardiomyocytes. Loss of this function by mutations or down-regulation of protein expression has been linked to hypertrophic cardiomyopathy, arrhythmias, and progression of disease in failing hearts. In this review, we summarize current views on the roles of JPH2 within the heart and how JPH2 dysregulation may contribute to a variety of cardiac diseases.

1. Introduction

Junctional membrane complexes (JMCs) are specialized subcellular domains found in striated muscle cells coupling transverse-tubule (T-tubule)-associated and intracellular sarcoplasmic reticulum (SR) ion channels. Within the heart, junctophilin-2 (JPH2) spans this junctional distance, tethering these two membrane structures to facilitate normal cardiac Ca^{2+} handling. Since the initial description of the membrane-coupling function of JPH2 within the heart, an extensive body of research has provided additional insights into a much more complex role of JPH2 in both cardiac function and disease.[1,2] In this review, we focus on the expanding role of JPH2 and its implications for future studies of JMC architecture and the role of JPH2 in cardiac disease. Specifically, we explore the importance of JPH2 in the postnatal development and maturation of T-tubules, the down-regulation of JPH2 in failing hearts and its role in pathological cardiac remodelling, the association of JPH2 mutations to inherited hypertrophic cardiomyopathy (HCM), and the newly established link of between JPH2 defects and arrhythmogenesis.

2. Importance of JMCs for cardiac excitation–contraction coupling

Within cardiomyocytes, the process of excitation–contraction coupling (ECC) is critical for coupling cellular depolarization and mechanical contraction. With depolarization, a small influx of extracellular Ca^{2+} through voltage-gated L-type Ca^{2+} channels (LTCCs) induces a larger efflux of Ca^{2+} from intracellular SR stores through type 2 ryanodine receptors (RyR2) in a process termed Ca^{2+}-induced Ca^{2+} release (CICR). This increase in cytosolic Ca^{2+} allows for mechanical cross-bridge formation and systolic myocyte contraction. This induced Ca^{2+} release through RyR2 also acts to inactivate the LTCC for efficient repolarization.[3] Upon diastolic relaxation, Ca^{2+} is sequestered back into SR stores by the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA2a) and extruded into the extracellular space through the Na^+/Ca^{2+} exchanger (NCX1).

In mature cardiomyocytes, ECC occurs in specialized subcellular domains known as JMCs where sarcolemmal invaginations termed T-tubules and the SR membrane are approximated. Within the ~12 nm cleft of JMCs, clusters of LTCC and RyR2 are functionally coupled facilitating the ion channel crosstalk in CICR.[4] Beyond functional coupling, studies suggest that LTCC may play a role in RyR2 gating either through a direct or indirect interaction.[5,6] In addition, the large cytosolic domains of RyR2 have been shown to be a scaffold for a number of proteins that modify its activity.[7]

3. The structural role of JPH2 in JMCs

In an unbiased immuno-proteomic study using isolated rabbit triad junctions to further characterize the emerging molecular complexity of

these microdomains, Takeshima et al.[2] identified JPH2 as a key molecule anchoring T-tubule and SR junctions. This important function was demonstrated in studies using JPH2 null mice which are embryonically lethal by Day E10.5 when the heart normally initiates contractile function.[2] There was a profound loss of JMCs in these mice, associated with spontaneous SR Ca^{2+} release and irregular Ca^{2+} transients. The weak, irregular contractions were attributed to the loss of coupling between LTCC and RyR2.

JPH2 has a unique structure, which enables this protein to approximate T-tubules to junctional SR.[1,2] At the N-terminus, eight highly conserved lipophilic 'Membrane Occupation and Recognition Nexus' (MORN) domains associate with the T-tubule sarcolemma.[1,8] The first six MORN domains are separated from the final two domains by a joining region. An α-helical domain spans most of the junctional space and is predicted to maintain the uniform spacing between the LTCC and RyR2. This is followed by an isoform-specific divergent region, which still maintains a high level of conservation across species. While the function of this region remains unknown, it serve a role in isoform-specific function and regulation. Finally, a C-terminal transmembrane domain embeds in the SR.[1] Identification of a novel JMC structural protein prompted further investigations into the role of JPH2 in both healthy and diseased hearts.

4. Role of JPH2 in the postnatal development of JMCs

Neonatal mammalian cardiomyocytes have a poorly developed cardiac T-tubule network.[9–11] Instead, they have an increased surface area-to-volume ratio and their myofibrils are located near the sarcolemma.[9,12] These features coupled with an increase in the expression and activity of the surface NCX allow for trans-sarcolemmal Ca^{2+} flux to adequately initiate ECC.[13] With increasing cell size, T-tubules develop within a few days after birth to maintain efficient ECC.[10,11,14–16] In this process of maturing Ca^{2+} signalling, T-tubule sarcolemmal invaginations approximate SR intracellular Ca^{2+} stores forming JMCs.

While the exact mechanism of these targeted membrane approximations remains unclear, several proteins have emerged to potentially play a role in tubulogenesis. For example, 'bridging integrator-1' (Bin1), also known as M-amphiphysin-2, has been shown to be a main factor in inducing membrane invaginations and trafficking of Ca^{2+} handling proteins in T-tubule biogenesis.[17–19] Altered splicing and mutations of Bin1 have been linked to peripheral myopathies.[20,21] Within Bin1, the highly conserved N-terminal Bin-Amphyphysin-Rvs (BAR) domain with a high affinity for phospholipids induces membrane tubulation both in vitro and in vivo in cells where tubulation is typically absent.[18,19,22,23] Bin1 also co-immunoprecipitates with LTCC and anchors microtubules at JMCs facilitating antegrade trafficking of this channel.[19] The down-regulation of Bin1 in failing hearts has been linked to mislocalization of LTCC.[24] Caveolin-3 (CAV3) whose expression localizes to invaginations of the cardiomyocyte sarcolemma called caveolae has also been shown to transiently associate with primitive T-tubules.[25] Several cardiac ion channels including the LTCC, various K^+ channels, and the voltage-gated sodium (Na^+) channel $Na_V1.5$ rely on caveolae-mediated localization.[26] In this way, multiple proteins play a role in T-tubule formation and channel localization.

Recently, our lab and other investigators demonstrated that JPH2, which also interacts with CAV3, plays an important role in the postnatal development of cardiac JMCs.[14,16,27] Independent studies utilizing acute

short-hairpin RNA (shRNA)-mediated knockdown of JPH2 in cultured rat cardiomyocytes showed T-tubule disorganization and an increased fraction of longitudinal T-tubule elements.[28,29] Furthermore, JPH2 expression initially co-localizing with LTCC coincides with the development of T-tubules with increased postnatal expression preceding the maturation of Ca^{2+} handling and gradual co-localization with RyR2 in developing JMCs.[15,28] Super-resolution microscopy in rat ventricular myocytes found a high level of correlation between RyR2 and JPH2 clustered into various similar well-defined shapes, although the molecular stoichiometry and role of JPH2 in forming these defined clusters remains unclear.[30]

Mice with cardiac-specific shRNA-mediated knockdown of JPH2 were unable to form mature T-tubules within the first few weeks of life, while Bin1 levels remained unchanged.[14,16] Conversely, T-tubule maturation occurred earlier in mice overexpressing JPH2 (Figure 1).[14] The disruption in maturation preferentially affected transverse elements suggesting longitudinal tubule elements may be JPH2-independent, which correlates with observed changes in T-tubule structure with JPH2 down-regulation in heart failure.[16] Taken together, these studies suggest that the development of T-tubules is a highly coordinated process involving numerous factors including JPH2 to induce membrane invagination, elongation, anchoring juxtaposed membranes, and protein trafficking.

5. Role of JPH2 in T-tubule remodelling in failing hearts

The pathological remodelling of T-tubule architecture has been described in both animal models and patients with failing hearts.[28,32–41] Recent evidence suggests that JPH2 is critical for the maintenance of JMCs and normal cardiac contractility. In vitro HL-1 cardiomyocytes with reduced levels of JPH2 have increased cell size and induction of several markers of pathological cellular hypertrophy and the foetal gene programme.[42] Mice with acute conditional cardiac sh-RNA-mediated knockdown of JPH2 have a high incidence of mortality with a rapid development of systolic heart failure.[43] These mice demonstrated grossly enlarged hearts with dilated ventricles and reduced systolic function on echocardiogram. In addition, JPH2 is down-regulated in a variety of cardiomyopathy animal models and patients. Initial observational studies in murine models of both HCM and dilated cardiomyopathy (DCM) showed down-regulation of JPH2 at the protein level, and additionally a decrease in JPH2 mRNA within the hypertrophic model.[27] Pressure-overloaded rats demonstrated a similar down-regulation of JPH2 expression with the onset of pathological hypertrophic remodelling and eventual heart failure.[29,44,45] The decrease in JPH2 mRNA levels was temporally associated with an increase in LV wall thickness and contractility, highlighting that down-regulation of JPH2 is an early event occurring during compensatory remodelling stages preceding overt heart failure.[29,44] Similarly, JPH2 expression is decreased in a murine model of myocardial ischaemia which is associated with loss of co-localization between JPH2 and RyR2 by super-resolution microscopy.[46] Finally, in patients with inherited HCM due to mutations in sarcomeric proteins, myocardium taken from septal surgical resection have demonstrated significantly reduced levels of JPH2.[42] While the loss of JPH2 has yet to be studied in patients with more diverse cardiac disease aetiologies, the disruption of T-tubule architecture occurs in ischaemic heart disease, idiopathic DCM, and HCM, and is likely a very early event in failing hearts.[29,41,46]
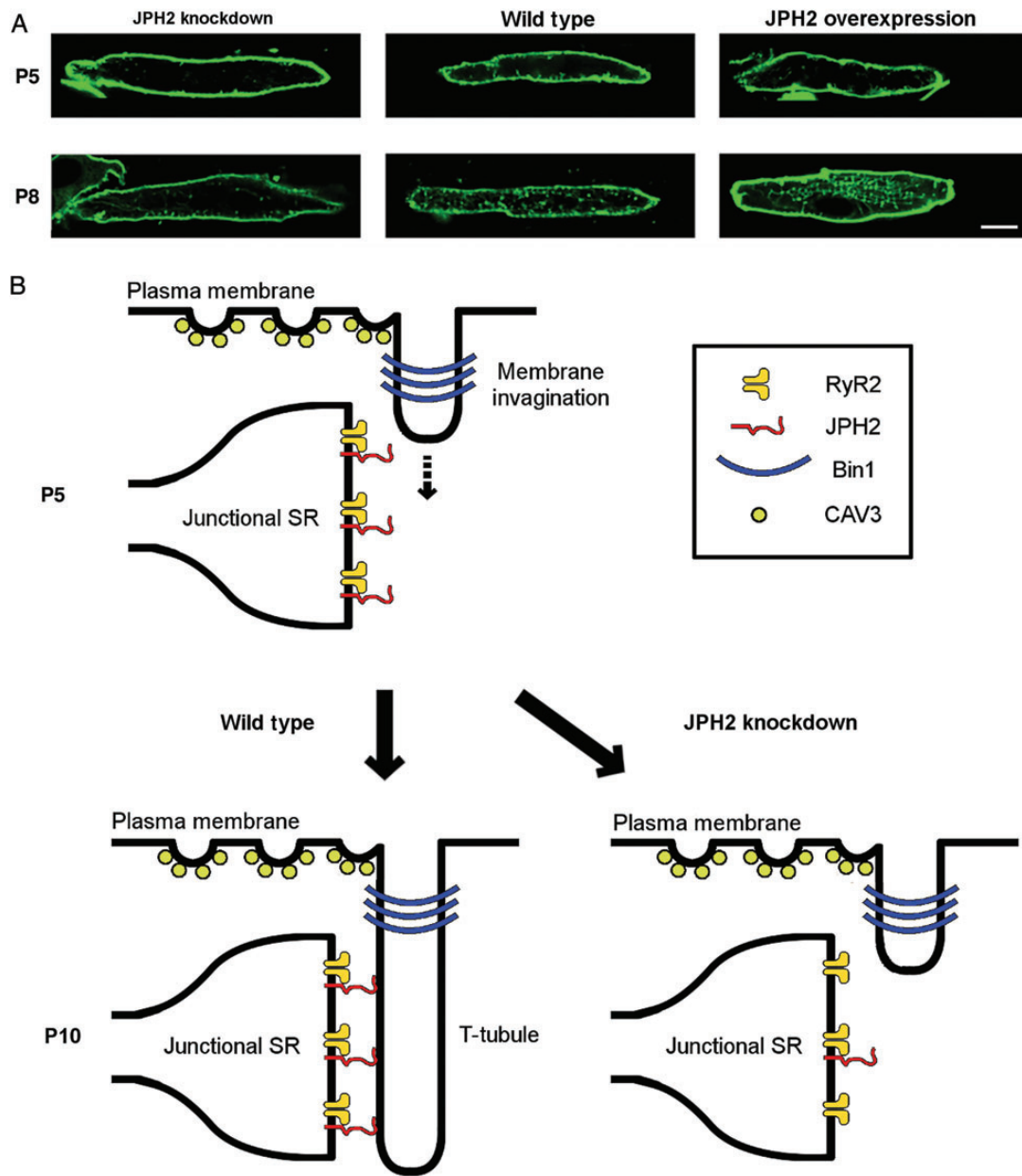
Figure 1 Positive correlation between JPH2 expression and postnatal T-tubule development. (*A*) Di-8-ANEPPS staining of ventricular myocytes isolated from JPH2 knockdown, wild-type, and JPH2 overexpression mice at P5 (before T-tubule maturation) and P8 (after initiation of T-tubule maturation) showing increased T-tubule development with increasing levels of JPH2. Scale bar = 10 μm. Adapted from Reynolds *et al.*[14] (*B*) Possible mechanism of normal T-tubule development involving CAV3, Bin1, and JPH2. The loss of JPH2 prevents anchoring of developing T-tubules to the SR and maturation Ca^{2+} of handling. Modified from Al-Qusairi and Laporte.[31]

The down-regulation of JPH2 expression may in fact underlie pathological cardiac remodelling. For example, mice with acute JPH2 knockdown exhibit a decrease in the total number of JMCs, whereas the remaining JMCs had an increased variability in spacing between the juxtaposed membranes.[43] In a rat heart failure model, reduced JPH2 levels led to decreased and displaced junctional SR surface area, and reduced length of the cardiac dyad.[45] With the down-regulation of JPH2, there is a decrease in transverse tubular structures and an increase in longitudinal structures, similar to changes in the development of perinatal T-tubule with loss of JPH2.[28,46] These observations could be consistent with the previously described regression to foetal gene expression and

architecture associated with cardiac pathology including compensatory hypertrophy.[47,48]

Recent studies have provided new insights into the molecular effects of JPH2 dysregulation in contributing to the defects in CICR and ECC in heart failure. Observing the disrupted CICR mechanism in failing rat hearts, an *in silico* model of disrupted JPH2-mediated structural integrity predicts scattered delay and weak Ca^{2+} transient generation.[45] This has been validated in a number of *in vitro* and *in vivo* studies. *In vitro* silencing of JPH2 blunted CICR with a decreased Ca^{2+} transient amplitude.[42] These findings were attributed to altered JMC function with RyR2 at its core since the expression of other Ca^{2+} handling and regulatory proteins

was unchanged. Furthermore, while the Ca^{2+} transient amplitude was decreased, SR Ca^{2+} levels were decreased to a relatively larger degree resulting in an increase in fractional SR release. This finding is in agreement with other models of heart failure which demonstrate a similar increase in fractional SR release.[49–51]

Subsequent investigation into the effects of induced JPH2 knockdown in adult mice found RyR2 hyperactivity with increased spark frequency due to mislocalization of LTCC and RyR2.[43] In addition, RyR2 was found to co-immunoprecipitate with JPH2 in murine cardiac tissue, suggesting that JPH2 regulates RyR2 gating and that a loss of JPH2 expression results in reduced ECC gain during CICR and increased RyR2 Ca^{2+} leakage during diastole. Similar interaction and gating effects between JPH2 and cardiac LTCC have not been seen, although JPH2 has been shown to possibly interact with the LTCC in skeletal muscle.[52]

In aortic-constricted rats, loss of JPH2 expression is associated with decreased sparklet-triggered spark-generation efficiency and increased spark latency, without alterations in myocyte fractional shortening, I_{Ca}, Ca^{2+} transient amplitude, or ECC gain during the period of compensatory hypertrophy.[44] Disruption of JMC architecture causes RyR2 to relocalize to non-JMC areas.[46] This mislocalization results in decreased Ca^{2+} release from the Ca^{2+} release unit, delayed and reduced Ca^{2+} transients, as well as increased RyR2 sparks and diastolic Ca^{2+} leak. The uncoupling of LTCC and RyR2 by disruption of T-tubule architecture caused by the down-regulation of JPH2 is emerging as a potential hallmark of heart failure progression (*Figure 2*).

Recent studies provided insights into the potential molecular mechanisms underlying the down-regulation of JPH2 in failing hearts. JPH2 was shown to be a direct target of microRNA-24 (miR-24) with two redundant binding sites in the 3′ untranslated region in the mouse, rat, and human homologues of JPH2.[53] miR-24 is up-regulated in rodent models of hypertrophy and heart failure, with coincidental down-regulation of JPH2, while other ECC proteins remained unchanged. miR-24 overexpression was associated with decreased CICR and reduced ECC gain most likely due to the decrease in JMC density and size observed in transmission electron microscopy imaging. Interestingly, administration of an miR-24 antagomir in a pressure-overload mouse model was able to preserve T-tubule architecture and normal Ca^{2+} signalling.[54] While suppression of miR-24 was not able to ameliorate hypertrophic changes, it did prevent the progression to decompensate heart failure.[54] Most recently, cardiomyocytes from patients with DCM and ischaemic cardiomyopathy were observed to have reduced

and mislocalized T-tubule–SR junctions with up-regulation of miR-24 and accompanying down-regulation of JPH2.[34] miR-24 belongs to the miR-23a,27a,24–2 cluster, which has been shown to be up-regulated by the calcineurin-nuclear factor of activated T-cell (NFAT) pathway active in adverse cardiac remodelling.[55] These studies provide a link between the pathways triggering pathological remodelling of the heart and disruption of T-tubule architecture and ECC.

A second mechanism of JPH2 regulation identified is that of Ca^{2+}-dependent proteolytic cleavage.[56] With sustained elevated levels of intracellular Ca^{2+}, μ-calpain was found to be autocatalytically activated, which was associated with truncation of JPH into a diffusible and fixed fragment. In skeletal muscle, this Ca^{2+}-induced cleavage was shown to correspond to loss of ECC gain. While this study mainly focused on proteolytic cleavage within skeletal muscle, calpain activity has been shown to be up-regulated in cardiac ischaemia–reperfusion injury.[53] Similar mechanisms of JMC disruption may be active within cardiomyocytes, although further investigation is merited.

Finally, a recent study identified a cytoskeletal transport mechanism for JPH2 mislocalization in T-tubule remodelling and failing hearts.[57] Microtubule stabilization and increased density is observed in hypertrophied and failing hearts and has been correlated with the loss of cardiac contractility.[58,59] In a murine model of pressure-overloaded hypertrophy, microtubule densification correlated with T-tubular remodelling and ECC loss. Furthermore, treatment of myocytes with a microtubule destabilizer, such as colchicines and nocodazole, disrupted T-tubular remodelling as well as JPH2 re-localization, which rescued efficient ECC. This has led to the hypothesis that kinesin anterograde trafficking of JPH2 away from the JMC may contribute to the loss of T-tubule integrity in failing hearts.[57]

6. Mutations in JPH2 associated with HCM

The first study to identify JPH2 mutations associated with human disease identified three mutations in patients with HCM.[60] In this study, three individuals among a largely Caucasian proband cohort of 388 North American HCM referrals hosted the unique mutations S101R, Y141H, and S165F, which localize to the amino terminus, first MORN motif domain, and the linker domain of JPH2, respectively.[60] Each of these probands demonstrated clear cardiac hypertrophy on echocardiogram and
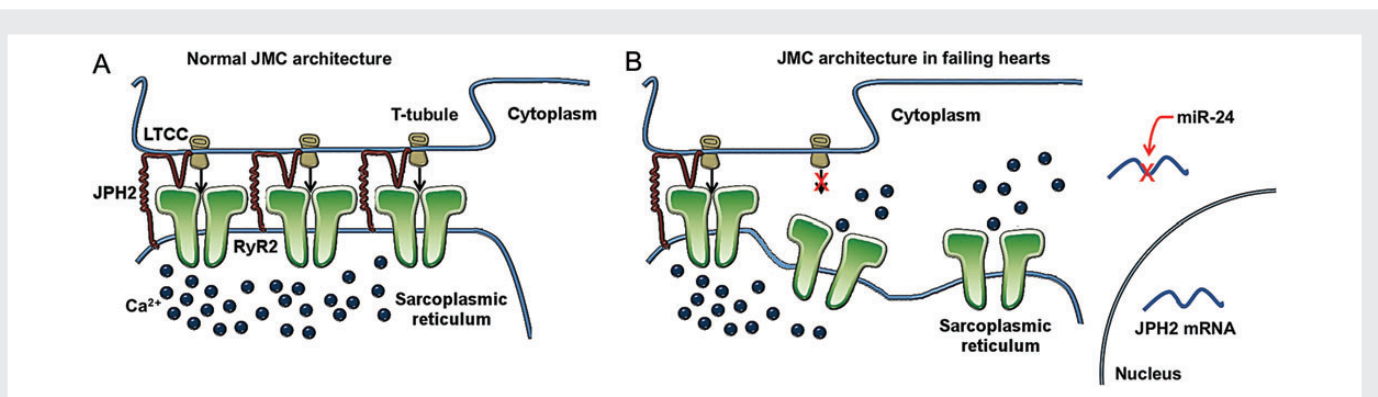
Figure 2 Defects in the JMC architecture with JPH2 down-regulation. (*A*) Normal coupling of LTCC and ryanodine receptors (RyR2) promoting efficient CICR (black arrows). (*B*) Down-regulation of JPH2 possibly due to up-regulation of miR-24 degradation of JPH2 mRNA leading to disruption of T-tubules and uncoupling of JMC-associated ion channels leading to decreased cardiac function. Model does not depict stoichiometric ratios.

were diagnosed with HCM, yet each was negative for mutations in the sarcomeric genes traditionally associated with HCM.[60] In keeping with previous studies, the JPH2-S101R, Y141H, and S165F mutations were found to reduce CICR amplitude and disrupt cellular ultrastructure utilizing *in vitro* myocyte models.[60] Furthermore, JPH2-Y141H and S165F were sufficient to induce cellular hypertrophy.[60] Subsequently, two additional genetic variants localizing to the divergent domain, JPH2-R436C and G505S, were reported in a small cohort of Japanese patients with HCM and were hypothesized to be associated with disease development.[61] Further genetic studies have cast doubt on the potential pathogenicity of these two mutations as each variant has been identified among cohorts of healthy individuals without HCM.[61,62] Furthermore, there have been no *in vitro* or *in vivo* studies to suggest functional impairment of JPH2 or the cardiomyocyte when these variants are expressed. In this way, these variants are likely to represent common polymorphisms without clinical significance.[63]

Recently, two additional JPH2 mutations were identified in individuals with HCM localizing to the linker and α-helical domains, respectively.[64] The JPH2-E169K mutation was identified in an Italian cohort of 203 index cases with HCM. This mutation was identified in a neonatally diagnosed proband with HCM as well as juvenile-onset atrial fibrillation (AF). This mutation was found to co-segregate with HCM and AF in a small, multigenerational pedigree.[64] Finally, the JPH2-A405S mutation (A399S in mice) was identified in an expanded cohort of North American Caucasian patients and was identified in a proband with HCM.[64] While the frequency of JPH2 mutations in patients with HCM remains low ($<1\%$), and a definitive causal link has not been established with such limited cases, these rare mutations have corroborated *in vitro* and murine studies involving JPH2 and have added additional insights into the role of JPH2 in a healthy and remodelled heart. More extensive genetic testing and the development of appropriate animal models expressing HCM-associated JPH2 mutations are needed to more clearly establish the link between these molecular defects and hypertrophic changes.

While the hypertrophic mechanisms associated with JPH2 mutations remains unclear, pathological cardiac hypertrophy has been linked to Ca^{2+}-dependent signalling pathways.[65] Several subcellular Ca^{2+}-handling domains have been implicated in initiating hypertrophic signalling, but work from our lab suggests that pathological RyR2 Ca^{2+} leak from the SR is sufficient to promote such remodelling.[66–72] This leak can activate the calcineurin/NFAT hypertrophic signalling pathway, in which the Ca^{2+}-sensitive phosphatase calcineurin activates NFAT nuclear translocation and hypertrophic gene transcription.[72,73] An increased RyR2 leak may also cause calmodulin-dependent kinase II (CaMKII) phosphorylation and calmodulin-dependent dissociation of histone deacetylase 4 (HDAC4) from myocyte enhancer factor-2 (MEF2), allowing this transcription factor to initiate hypertrophic signalling.[71,74] Future studies are needed to determine whether JPH2 mutations and JPH2 down-regulation cause similar defects in JMC Ca^{2+} handling and activate canonical hypertrophic pathways, or if these HCM-associated mutations will provide insights to novel mechanisms of hypertrophy.

7. Defective JPH2-mediated regulation of RyR2 may contribute to arrhythmogenesis

Observing that the HCM-associated JPH2-E169K mutation was uniquely associated with the development of early-onset AF, our lab recently elucidated a novel mechanism associating JPH2 and arrhythmogenesis.[64] Correlating well with clinical findings in a small multigenerational family hosting the mutation, heterozygous JPH2-E169K mice had a higher incidence of pacing-induced AF secondary to abnormal spontaneous Ca^{2+} waves and increased spark frequency. This RyR2-mediated Ca^{2+} leak was a result of a decrease in the direct stabilizing interaction between RyR2 and JPH2.[43,64] Indeed, JPH2-E169K demonstrated reduced RyR2 binding as well as increased RyR2 spark frequency and Ca^{2+} leakage. This contributed to increased diastolic Ca^{2+}, which can activate the sarcolemmal NCX and create a net depolarizing current causing delayed after depolarizations (DADs).[75,76] DADs underlie the most significant mechanism of atrial arrhythmias.[77]

Broadening the implications of JPH2 dysregulation in the pathogenesis of arrhythmias, total JPH2 expression levels were shown to negatively correlate with the incidence of AF in mice.[64] Addition of a small 25 amino acid JPH2 peptide mimicking the E169 region stabilized RyR2 in cardiomyocytes isolated from JPH2-deficient mice. These observations in murine models were corroborated in patients with paroxysmal AF, who were found to have a decreased JPH2:RyR2 ratio and a resulting increase in both Ca^{2+} sparks and spontaneous Ca^{2+} waves.[64] In this way, arrhythmogenic SR Ca^{2+} leak may be triggered by loss of the RyR2-stabilizing interaction of JPH2, and either loss of function JPH2 mutations or down-regulation of JPH2 expression may lead to arrhythmia predisposition (*Figure 3*). Although the T-tubule network is less extensive or minimally present in some species, T-tubule are thought to play a role in synchronizing Ca^{2+} release in particular in large mammals and humans.[33] At this time, it is not known yet whether the JPH2 mutation impacts T-tubule architecture in the atrial myocytes of the mutation carriers.

Decreased RyR2 stability by increased SR Ca^{2+} load or intrinsic channel modification is extensively linked to arrhythmogenesis.[75,76,78,79] Excessive SR-free Ca^{2+} content, whether by decrease in calsequestrin Ca^{2+} buffering capacity or increased SERCA activity, promotes RyR2 diastolic Ca^{2+} leak.[75,80,81] Hyperphosphorylation of RyR2 at S2808 and S2814 by protein kinase A (PKA) and Ca^{2+}/CaMKII, respectively, increases channel open probability and is observed in AF.[79,82,83] Conversely, dysregulation of phosphatase activity by the phosphatase inhibitor I-1 can also promote RyR2 hyperphosphorylation in patients with arrhythmia.[84] Loss of the RyR2 inhibitory protein FK506-binding protein 12.6 (FKBP12.6) from the RyR2 complex by PKA phosphorylation or inherited arrhythmia-associated RyR2 mutations increases channel activity and promotes susceptibility to arrhythmogenesis.[85,86] While the timeline and complexity of molecular remodelling in arrhythmogenesis remains unclear, these studies suggest that loss of RyR2 stability is central to arrhythmogenesis and JPH2s, structural maintenance of JMCs and regulatory role on RyR2 and perhaps other JMC-associated proteins are critical for normal cardiac Ca^{2+} handling.

In addition to regulating RyR2 gating and SR Ca^{2+} leak, it is also possible that JPH2 modulates the function of other channels. In skeletal muscle, the transient receptor potential channel canonical type 3 (TRPC3) modulates the function of RyR1 through binding with JPH2.[87] Skeletal muscle JPH2 has been shown to directly interact with TRPC3 near the joining region of JPH2, and the JPH2-S165F mutation abolishes protein kinase C-mediated phosphorylation resulting in reduced binding to TRPC3.[88,89] Overexpression of the JPH2-S165F mutation in primary murine skeletal myotubes resulted in hypertrophy, reduced CICR, and reduced SR Ca^{2+} release via RyR1.[90] While a similar interaction between TRPC3 and JPH2 in cardiac tissue has not
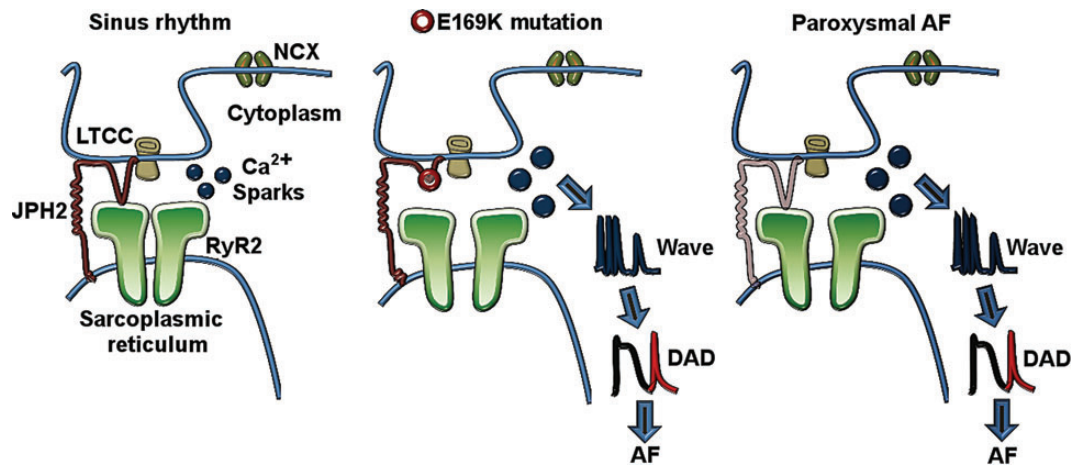
Figure 3 Proposed mechanism of JPH2-linked RyR2 dysregulation in AF. (Left panel) Normal cardiac JMC structure and Ca^{2+} handling. (Center panel) Loss of stabilizing interaction between RyR2 and JPH2 by the E169K JPH2 mutation causes increased RyR2 diastolic Ca^{2+} leak causing depolarizing waves, DADs, and triggered AF. (Right panel) A decreased ratio of JPH2:RyR2 causes similar RyR2 gating instability leading to AF.

been demonstrated to date, the close proximity of the JPH2-S165F mutation and E169K mutations raise the possibility of an analogous regulatory role.

8. Conclusions

JPH2 has emerged as a critical regulator of the complex JMC microenvironment in cardiac myocytes. It provides an anchor for developing T-tubules during maturation of cardiac Ca^{2+} handling, is a molecular tether between T-tubules and junctional SR, and has regulatory functions on local ion channels and intracellular Ca^{2+} signalling. Further studies will be needed to more completely describe critical or novel JPH2 interactions, post-translational modifications, and regulation both in healthy and diseased hearts. Since JPH2 expression levels are disrupted in a variety of cardiac pathologies, preservation of its function might prevent the development or progression of these diseases. While the full extent of the role of JPH2 in human cardiac disease remains unclear, this work may provide a path forward towards future targeting strategies aimed at preventing or reversing adverse cardiac ultrastructural remodelling.

Conflict of interest: none declared.

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