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Review article

Cardiac connexins and impulse propagation

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ABSTRACT

Gap junctions form the intercellular pathway for cell-to-cell transmission of the cardiac impulse from its site of origin, the sinoatrial node, along the atria, the atrioventricular conduction system to the ventricular myocardium. The component parts of gap junctions are proteins called connexins (Cx), of which three main isoforms are found in the conductive and working myocardial cells: Cx40, Cx43, and Cx45. These isoforms are regionally expressed in the heart, which suggests a specific role or function of a specific connexin in a certain part of the heart. Using genetically modified mice, the function of these connexins in the different parts of the heart have been assessed in the past years. This review will follow the cardiac impulse on its path through the heart and recapitulate the role of the different connexins in the different cardiac compartments.

Contents

1. Introduction

Every normal heartbeat is initiated in the sinoatrial node, conducted along the atria, delayed at the AV-node, after which the ventricular myocardium is activated via the specialized conduction system. After activation, the impulse is conducted from myocyte to myocyte along the entire myocardium.

The process of impulse conduction is governed by three factors: (1) excitability of single cardiomyocytes, (2) electrical coupling between myocytes, and (3) network properties of cardiac tissue [1]. Excitability of single myocytes is determined by the amount of sodium current, which not only generates the depolarizing current for local cellular activation, but also for activation of adjacent cells by passing depolarizing current through gap junctions. Impulse propagation is dependent on multiple factors, in which the interaction between inward currents, such as I_{Na} and I_{Ca}, electrical coupling, cell size, resting potential and input impedance are involved [2–5]. This review will focus on the role of gap junctions in impulse conduction in the heart under physiological and pathophysiological conditions.

2. Cardiac gap junctions

Gap junctions were named after their appearance in transmission electron microscopy. At the interface of two adjacent cells, the two membranes are separated by an electron-dense structure with a characteristic gap of 2–3 nm.

Each gap junction channel is composed of two hemichannels, also called connexons, one provided by each cell. Two connexons of adjoining cells pair to form a functional channel, which connects the cytoplasms of both cells (Fig. 1, upper panel). Connexons are hexamers of proteins called connexins. At present, more than 20 connexin genes have been identified in mouse and human [6,7]. They are named after their theoretical molecular mass. The molecular structure of the connexins is very similar among all members. They all

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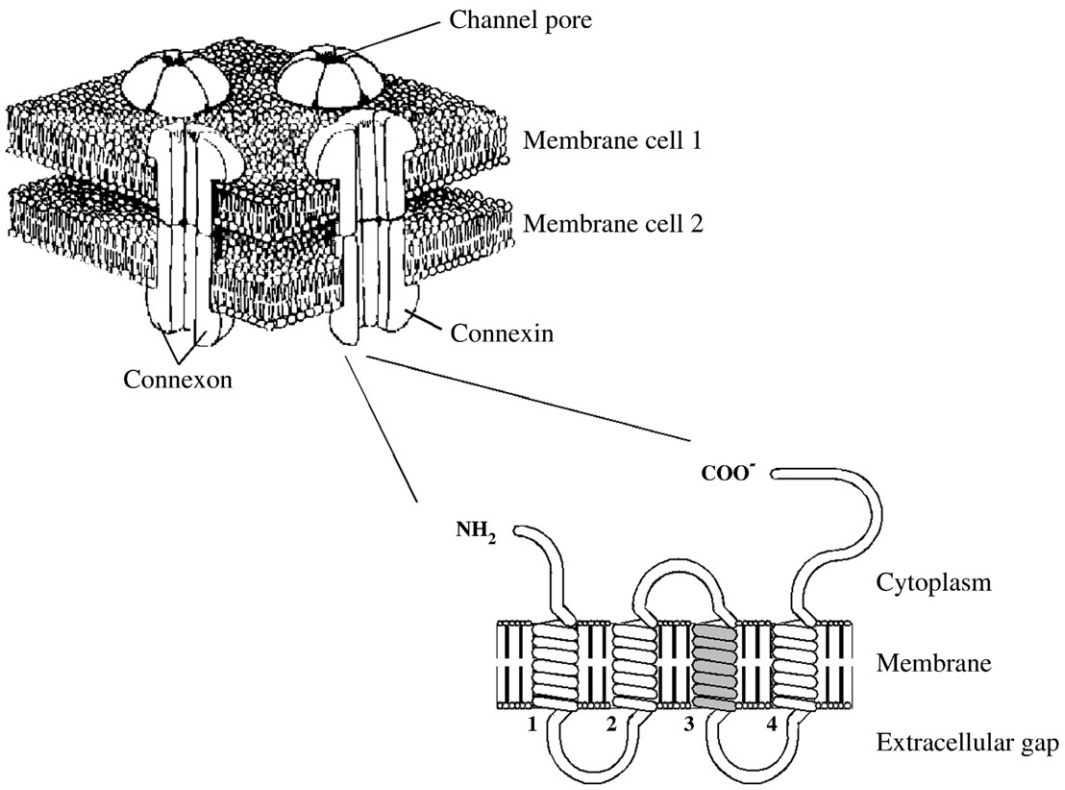

Fig. 1. Artists impression of a gap junction plaque. Every gap junction channel is composed of two connexons, each of which is composed of six connexins. Adapted from [8].

have four membrane spanning domains, two extracellular loops and the amino- and carboxy-terminus, which are located at the cytoplasmic side (Fig. 1, lower panel). Although very similar in structure, the biophysical properties of the channels formed by different connexin family members are very different [8,9].

In the heart, three main isoforms are found in the conductive and working myocardial cells: Cx40, Cx43, and Cx45. Fig. 2 shows the regional expression of these Cxs in the mouse heart. Cx40 is mainly expressed in the atrial myocytes, in the AV-node, His-bundle and the ventricular conduction system [10–15]. Cx43 is by far the most abundant and is expressed between atrial and ventricular myocytes and distal parts of the conduction system [12,15–23]. The expression of Cx45 is mainly localized in the sinoatrial node (SAN), the atrioventricular node (AVN), His-bundle and bundle branches [15,24–27]. Low levels of Cx45 were also detected in atrial and ventricular myocytes [28,29], although other studies, using different antibodies, were not able to confirm these findings [24].

In mice, a fourth connexin is found, i.e., Cx30.2 which is expressed in the SAN, AVN and His-bundle [30]. Since the human orthologue of Cx30.2, Cx31.9, was detected in the human heart, Cx30.2 may represent a mouse specialization [31].

Gap junctions between ventricular myocytes are expressed in a polarized way. Gap junctions are mainly localized at intercalated disks and have relatively low density at lateral sides [22,23,32–35]. The intercalated disk region itself is a highly three-dimensional structure, in which gap junctions connect adjacent cells both in the plicate (regions perpendicular to the long axis of the cells) and interplicate regions (those more or less parallel to the long axis of the cells). Several studies suggest that gap junctions are more abundant in the interplicate regions than in the plicate regions [32,35–41]. It seems

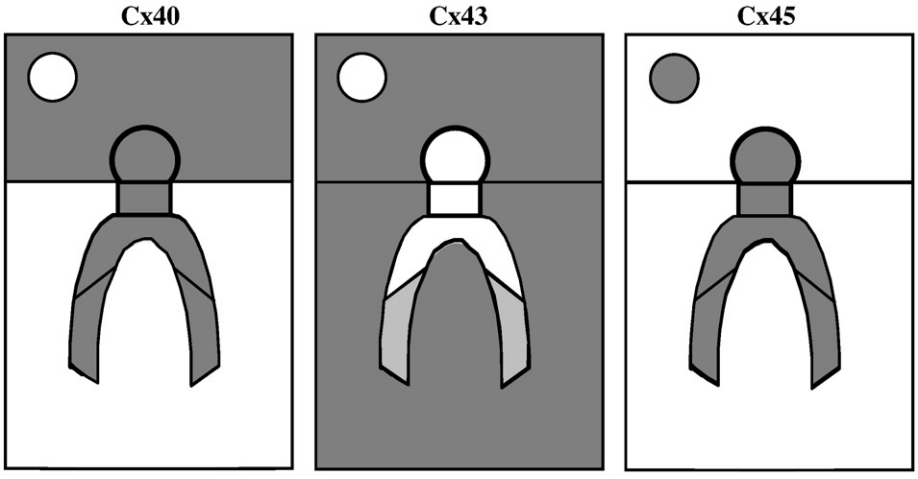

Fig. 2. Chamber specific expression of Cx40, Cx43, and Cx45 in the mouse heart (redrawn after [84]).

that the gap junctions in the interplicate regions are also involved in transverse conduction.

The role of the individual cardiac connexins has been extensively studied in genetically modified mouse models, in which one or more connexins were partly or fully absent. However, because most cardiac connexins are expressed in multiple cell types in the heart, we will follow the cardiac impulse on its path through the heart and recapitulate the role of the different connexins in the different cardiac compartments.

3. Connexin function in the sinoatrial node

In the SAN, gap junctions are responsible for two main functions: (1) maintaining regular beating frequency and (2) transferring the impulse to the atrial myocardium in the face of the hyperpolarizing atrial load [42]. Only little coupling is needed for synchronization of both frequency and waveform of individual SAN cells, thereby averaging out the small differences in intrinsic frequency and action potential shape [43]. The issue of transfer of the electrical impulse to the atrial myocardium is not fully resolved yet. Early model studies have shown that a gradual increase in electrical coupling would be prerequisite for successful conduction of the generated impulse from SAN to the atrial myocardium [44,45]. Immunohistochemical studies have shown that in the center of the SAN, Cx45 is the predominant gap junction protein, although Cx40 was also found, while in the peripheral parts, Cx40 and/or Cx43 are expressed [10,25,26,46], but some controversy exists. For an extensive review see Boyett et al. [47]. No clear gradient was found, but interestingly, interdigitation of strands of Cx43 expressing atrial myocytes and SAN cells were found, which may serve as transitional zone [26,48]. Jongsma hypothesized that heterotypic gap junctions formed one Cx43-connexon and one Cx45-connexon, which have been shown to exhibit rectifying properties [49], may close when current flows from the atria to the SAN, while facilitating current flow from SAN to atrium [42]. In this way, the specific expression of Cxs may support SAN function.

Studies using mice knockout for Cx43 or Cx45 did not reveal significant sinus node abnormalities. $Cx40^{-/-}$ mice displayed leading pacemaker activity as breakthrough activation at the base of the sulcus terminalis, RA free wall, and right superior vena cava, rather than at the sinoatrial node as found in wildtype mice. In $Cx40^{-/-}$ mice, heart rate was mostly normal [50–55], although some slowing was observed [56,57]. Haploinsufficiency for Cx45 alone or combined with Cx40 deficiency had no effect on heart rate [58]. Similarly, the absence of Cx30.2 alone, or combined with Cx40 deficiency resulted in normal sinus node function [59]. Finally, haploinsufficiency for or full deletion of Cx43 did not alter sinus node function [60–64].

Overall, the sinoatrial node function seems fairly robust, even when apparently essential connexins are expressed in reduced amounts. This fits well with the fact that only little amount of coupling is needed for synchronization within the sinus node [43]. Moreover, the current-to-load mismatch between the sinus node and the atrium would presumably benefit from reduced levels of intercellular coupling [65].

4. Atrial connexins

In the atria, three types of connexins are expressed, i.e. Cx40, Cx43, and Cx45. The expression level of Cx45, however, is very low [29]. In human atria Cx43 expression was found to be similar between human LA and RA, but Cx40 levels were higher in RA compared to LA [29]. In goats however, Cx40 content was lower in RA, compared to LA, while Cx43 levels were similar between both chambers [66].

Functional measurements were performed on mice which were deficient for Cx43 or Cx40. These measurements involved ECG measurements and epicardial conduction velocity measurements. Total atrial activation times are reflected in the P-wave of the ECG, but are not only determined by atrial impulse conduction velocity, but also by the pattern of impulse spread and atrial size.

Mouse models haploinsufficient for Cx43 or conditional knockouts for Cx43 showed no significant changes in P-wave duration [61,64,67] or atrial conduction velocity [61]. These studies indicated that Cx43 is not the dominant connexin for atrial conduction in the presence of Cx40.

To unravel the role of Cx40 in atrial conduction, many studies have been performed on Cx40 KO mice. As a general finding, haploinsufficient Cx40 KO mice were indistinguishable from wildtype mice [50,51,55,57].

ECG recordings on homozygous Cx40 KO mice exhibited prolonged P-wave duration [50–52,55,57], which is compatible with the detected reduced right-atrial conduction velocity [52,55]. However, prolongation of the P-wave was not a common finding, as in other studies, a P-wave prolongation was not found [53,54,56]. Moreover, Cx40 KO mice were more vulnerable to supraventricular arrhythmias [55,57].

Some studies have shown that absence of Cx40 during development may result in cardiac abnormalities and malformations, such as cardiac hypertrophy in conjunction with common atrioventricular junction or a ventricular septal defect [68]. This developmental aspect may not be recognized in other studies and can therefore partly be responsible for the observed conduction abnormalities. Alternatively, the different genetic background may be an important modulator in the developmental abnormalities in Cx40 KO mice, which determines the presence or absence of malformations.

An unexpected finding is the relationship between atrial impulse conduction and the ratio of Cx40 and Cx43 expression. Kanagaratnam et al. showed that right atrial conduction velocity in humans was *inversely* related to the ratio $Cx40/(Cx40+Cx43)$, but linearly related to $Cx43/(Cx40+Cx43)$ [69]. Interestingly, conduction velocity was not related to Cx43 levels or total Cx $(Cx40+Cx43)$ levels. These findings were confirmed by Beauchamp et al. in cultured strands of atrial myocytes derived from mice with genetic deficiency for Cx40 or Cx43 [70]. Relative abundance of Cx40 decreased conduction velocity, while dominance of Cx43 increased conduction velocity.

Studies in exogenous expression systems have shown that gap junctions composed of Cx40 hemichannels and Cx43 hemichannels (homomeric/heterotypic) are not compatible [71–73] or form gap junctions with much lower total conductance [74]. In atrial myocytes, where Cx40 and Cx43 are coexpressed in the same gap junctions [69,75], heteromeric/heterotypic channels may theoretically be formed. The presence of both Cx40 and Cx43 in the same hemichannel channels was confirmed [76,77], but it is not clear whether such channels are truly functional. Some studies suggested the functional presence of heteromeric/heterotypic Cx40/Cx43 channels [78], while others showed that these channels are presumably functionally insignificant [77]. Taken altogether, the coexpression of Cx40 and Cx43 is associated with reduced intercellular conductance, which may explain the findings by Kanagaratnam and Beauchamp.

In the previously mentioned studies, haploinsufficiency for Cx40 was not associated with increased conduction velocity, which may be due to specific expression patterns in adult mouse myocytes [70].

The most common arrhythmia in humans is atrial fibrillation [79]. A common finding in animal models and human atrial fibrillation is abnormal expression and distribution of atrial Cx40. The literature on this subject is vast and several reviews have focused on this issue [80–83]. Such abnormal expression levels and patterns of Cx40 may lead to inhomogeneous electrical coupling resulting in dispersed conduction, which forms the substrate for atrial arrhythmias.

5. Connexins and atrioventricular conduction

In the atrioventricular conduction system of mice, three types of connexins have been described, Cx40, Cx30.2, and Cx45

[10,30,51,59,84–86]. Cx31.9, the human orthologue for Cx30.2 is presumably not expressed in the human AV-node [31], and Cx30.2 may therefore reflect a mouse specialization.

The absence of Cx40 was consistently associated with abnormal AV-conduction, i.e., prolonged PQ intervals and QRS duration [50–52,54–59]. The prolongation of the PQ interval was mainly located in the his-ventricle (HV) interval [59], but some reported a prolonged atrial-his (AH) interval as well [54,56].

A typical finding was the delayed activation of the ventricles as detected by QRS widening and fractionation [50–59]. Verheule et al. elegantly showed that this prolonged QRS duration was only present during anterograde activation of the ventricles, but not during ventricular pacing at the apex [55]. Conduction velocity in the ventricles of Cx40 KO mice was normal [53,55], and the QRS-widening was attributed to abnormal conduction in the bundle branches of Cx40 KO mice. In the right bundle branch (RBB) slow conduction [53] or conduction block [87] was reported. In the left bundle branch, conduction was slowed by 33% [87].

The relative role of Cx45 in atrioventricular conduction was investigated in mice haploinsufficient for Cx45 in the presence or absence of Cx40 [58]. Haploinsufficiency for Cx45 alone did not affect atrioventricular conduction, as PQ and QRS duration was similar to control [58]. Full deletion of Cx45 was not studied, because homozygous deficiency for Cx45 is lethal due to defective vascular development [88,89]. Interestingly, in the absence of Cx40, which by itself prolongs PQ and QRS duration, additional haploinsufficiency of Cx45 further delays atrioventricular conduction and ventricular activation [58].

The last atrioventricular connexin, Cx30.2 has an intriguing role. Cx30.2 is expressed in the atrioventricular node and His-bundle [30]. Mice knockout for Cx30.2 exhibited a decreased PQ duration, indicating *increased* atrioventricular conduction [90]. This decrease in AV delay was attributable to decreased AH, but not HV intervals, indicating increased supraHisian conductivity [90]. Mice double deficient for Cx40 and Cx30.2 showed normal AH and HV intervals. Schrickel et al. concluded that in the atrioventricular conduction system, Cx45 is sufficient for impulse propagation in the AV node, where Cx40 and Cx30.2 act as counterparts which increase or decrease conduction velocity, respectively [59].

6. Ventricular connexins

In the ventricular myocardium, Cx43 is the main connexin. Cx43 KO mice died perinatally, due to a cardiac malformation of the pulmonary outflow tract [91–93]. Cx43 haploinsufficient and conditional knockout mice have been generated and analyzed.

A 50% reduction in Cx43 expression ($Cx43^{+/-}$ mice) was found to result in an increased activation delay of the ventricles and reduced conduction velocity [60,61,94,95]. In other studies, however, a similar 50% reduction of Cx43 expression did not alter conduction velocity in the mouse heart [62,96].

Because the perinatal death of $Cx43^{-/-}$ mice prevented analysis of conduction in those hearts, conduction was determined in strands of ventricular myocytes from germline $Cx43^{-/-}$ mice. In strands of $Cx43^{+/-}$ myocytes, Cx43 protein expression was reduced by 43%, but conduction velocity was unchanged [97]. The same group showed that in strands of $Cx43^{-/-}$ ventricular myocytes, Cx43 expression was absent and conduction velocity was reduced by 96% [98]. This very slow conductance was dependent on the presence of low levels Cx45.

To obtain a mouse model with more than 50% Cx43 protein reduction without perinatal lethality, several conditional Cx43 knockout mouse models based on the Cre/LoxP system were generated. In one study, expression of the Cre enzyme was driven by the α-myosin heavy chain (αMHC) or myosin light chain 2v (MLC2v) promoter [63]. The mice developed normally, but died suddenly within 2 months after birth. A selective bred, selecting for progressively older αMHC-Cre/$Cx43^{fl/fl}$ mice, resulted in mice with a more gradual loss of Cx43 and prolonged lifespan (up to 300 days) [67]. In another model, one coding region of the Cx43 gene was replaced by Cre-ER(T), a fusion construct of the Cre recombinase and a specifically mutated version of the ligand binding domain of the human estrogen receptor [99]. The second Cx43 region was floxed and deletion was induced by injection of 4-hydroxytamoxifen (4-OHT; $Cx43^{CreER(T)/fl}$ model) [64]. This resulted in sudden death of all induced $Cx43^{CreER(T)/fl}$ mice within 1 month after the induced deletion [64].

The general outcome of the studies on the conditional Cx43 KO models is that ventricular conduction slowing and ventricular arrhythmias become prominent only when Cx43 levels drop to levels below 20% of control [63,67,96]. At these low levels, Cx43 expression was found to be heterogeneous [63,67,96]. Telemetric recordings revealed lethal ventricular tachyarrhythmias [63,64]. Epicardial mapping showed that conduction slowing was more prominent transverse to myocardial fiber direction (CV_{trans}) than in the longitudinal direction (CV_{long}) [63,96] and that the right ventricle is more sensitive to Cx43 changes than the left [96]. Arrhythmias were induced during epicardial mapping, which originated from the RV, showing stable anisotropic reentry and fibrillatory conduction on the LV [96].

The intriguing outcome of the Cx43 conditional KO studies was that even at very low levels of Cx43, conduction was maintained at ~50% of normal velocity. These observations compare well to studies performed *in silico* which showed that the relationship between junctional conductance and conduction velocity was nonlinear, and very substantial reductions were required for conduction slowing [100,101]. During uncoupling, conduction slowing was paralleled by two other changes: (1) increasing safety factor and (2) increased action potential upstroke velocity (Vmax). (1) Safety Factor (SF) describes the relationship between activated cells acting as current source and current sinks, which are the cells that receive the current for activation. For a detailed explanation please refer to [1]. If the amount of source current exactly matches the required sink current, SF equals 1. A SF>1 means that more current is generated during excitation than needed for exciting the sink cells. If SF<1 conduction block occurs. Computer modeling and *in vitro* studies showed that mild uncoupling increases SF, and can sustain very slow conduction successfully; however, a high level of uncoupling reduces SF and results in conduction block [2,102]. (2) The second *in silico* finding during uncoupling was an increased Vmax [100]. This was also reported during experiments *in vivo* [103] and *in vitro* [97,98]. These combined findings fit well in the concept of 'discontinuous conduction' in the heart. This concept is explained well by Spach: 'At the microscopic level, there are recurrent discontinuities of intercellular resistance, which in turn alter the membrane ionic currents by means of electrical loading' [104]. In cardiac reparations, Vmax was dependent on the direction of conduction and was, apparently paradoxical, larger during slow conduction in the high resistive direction perpendicular to myocyte orientation. Vmax was lower parallel the long and low resistive axis of the myocytes [4]. In conclusion, partial or substantial uncoupling may lead to slowed conduction with higher safety, but may be partly counteracted by concomitant increase of Vmax.

Virtually any type of ventricular remodeling, due to cardiac overload is characterized by changes in the expression and distribution of Cx43. The first reports on gap junction remodeling in human cardiac disease involved lateralized and reduced Cx43 expression with fiber disarray in the infarct border zone [40,41,105]. In hypertrophic cardiomyopathy, early compensated hypertrophic remodeling resulting from aortic stenosis was correlated with a strong increase in Cx43 expression with extensive lateral staining

[106]. Interestingly, Cx43 expression was reduced and heterogeneously distributed without lateralization in more progressive decompensated stages of this disease [106]. Other studies have shown that in humans, hypertrophic cardiomyopathy (HCM) can be related to downregulation of Cx43 without lateralization [40] or to lateralization without changes in Cx43 levels [35]. Dilated cardiomyopathies in humans are reported to be linked to reduced Cx43 expression, mostly with a lateralized expression pattern [107–110]. In patients with DCM, those with VT showed a heterogeneously reduced expression of Cx43 compared to those without VT [107]. In the case of ischemic cardiomyopathy, the infarct border zone, the myocardial zone located directly next to the infarct scar, is most subject to remodeling.

7. Concluding remarks

Gap junctions formed of various connexins form the intercellular pathway for transmission of the cardiac impulse from the sinoatrial node to the ventricular myocardium. The chamber specific expression and function of connexin isoforms is also reflected by the pathophysiological changes. Abnormal Cx40 expression is associated with atrial fibrillation, while abnormal Cx43 expression in the ventricle is associated with ventricular arrhythmias.

However, changes in gap junction expression alone are presumably not sufficient for conduction slowing and enhanced arrhythmogeneity. The observed reduction in, e.g., Cx43 expression in patients with ventricular remodeling ranges between 30% and 50% [36,106,109–112]. Mouse experiments have shown that such changes do not necessarily lead to reduced conduction velocities [62,96]. With regard to connexins, there is a large 'conduction reserve' [113–115], the myocardium is able to maintain near normal conduction velocities, even when electrical coupling is substantially reduced. Interestingly, this conduction reserve also applies to other determinants of impulse conduction. Besides changes in connexin expression, ventricular remodeling is also characterized by reduced excitability (impaired sodium channel expression and function) [116–118], and increased intercellular collagen deposition (fibrosis) [119–121]. Experiments in mice have shown that such clinically relevant, isolated reductions in sodium channel expression or increased fibrosis only have minor effect on impulse conduction, while their combination severely slowed conduction [122]. Recently, we have shown that a 50% reduction in Cx43 expression is very arrhythmogenic when combined with increased fibrosis [123], but not in combination with decreased sodium channel function [124]. Therefore, to explain abnormal conduction and arrhythmogenesis in cardiac disease, the description of aberrant connexin expression alone is presumably not sufficient. Conversely, if other factors combined with reduced coupling are needed, restoring one may be sufficient to normalize conduction and reduce arrhythmogeneity. As such, strategies aiming for improved gap junctional coupling may be antiarrhythmogenic. An example of such strategy is the use of antiarrhythmogenic peptides (AAP10, ZP123, Rotigaptide) which were shown to reduce atrial fibrillation [125,126], and ventricular tachycardia during myocardial ischemia in dogs [127], although their beneficial effect in explanted human failing hearts was not straightforward [128]. These peptides presumably act by modulating Cx43 phosphorylation [129–131]. Cx43 is a phosphoprotein, and the level of phosphorylation is implicated in the regulation of electrical coupling [9]. Under normal conditions in the heart, Cx43 is phosphorylated [132], but becomes dephosporylated leading to uncoupling under pathological conditions, such as ischemia [133] and heart failure [134]. Direct suppression of Cx43 dephosphorylation resulted in improved coupling [134].

Finally, post-transcriptional mechanisms, such as the microRNA miR-1, were shown to regulate Cx43 expression and arrhythmogenesis in health and disease [135] and may therefore also be a potential antiarrhythmic target.

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