Cardiac Sodium Channel Na\text{\textsubscript{v}}1.5 and its Associated Proteins

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Summary

The main cardiac voltage-gated Na\textsuperscript{+} channel, Na\textsubscript{v}1.5, plays a key role in generation of the cardiac action potential (cardiac excitability) and propagation of the electrical impulse in the heart (cardiac conduction). During the past decade, numerous mutations in SCN5A, the gene, encoding Na\textsubscript{v}1.5, were found in patients with different pathologic cardiac phenotypes such as the congenital long QT syndrome type 3, Brugada syndrome, and progressive cardiac conduction defect (or Lenègre-Lev disease). These mutations define a sub-group of Na\textsubscript{v}1.5 / SCN5A-related cardiac channelopathies. Recent works have suggested that Na\textsubscript{v}1.5 is part of several multi-protein complexes located in different membrane compartments of the cardiac cells. In some instances, the genes of these regulatory proteins were also found to be mutated in patients with inherited forms of cardiac arrhythmias. The proteins that associate with Na\textsubscript{v}1.5, and form these complexes, can be classified as 1) anchoring/adaptor proteins, 2) enzymes interacting with and modifying the channel, and 3) proteins modulating the biophysical properties of Na\textsubscript{v}1.5 upon binding. The purpose of this short article is to review the proposed roles of these interactions.

These recent observations indicate that the expression level, cellular localization, and activity of Na\textsubscript{v}1.5 are finely regulated by complex molecular mechanisms that we are only starting to elucidate.

Résumé

Le canal sodique cardiaque Na\textsubscript{v}1.5 et ses protéines associées

Le canal sodique cardiaque dépendant du voltage, Na\textsubscript{v}1.5, joue un rôle essentiel dans la génération du potentiel d’action cardiaque (excitabilité cardiaque) et dans la propagation de l’activité électrique (conduction cardiaque). Durant les dix dernières années, un grand nombre de mutations du gène SCN5A (qui code pour Na\textsubscript{v}1.5) ont été décrites chez des patients atteints de nombreux phénotypes cardiaques différents : syndrome du QT long congénital du type 3, syndrome de Brugada, bloc de conduction progressif (maladie de Lenègre-Lev). Ces phénotypes définissent le groupe des canalopathies dues à Na\textsubscript{v}1.5 / SCN5A. Des travaux récents démontrent que Na\textsubscript{v}1.5 fait partie de complexes multi-protéiques localisés dans différents compartiments des cellules cardiaques. Dans certains cas, les gènes qui codent pour ces protéines régulatrices ont été trouvés mutés chez des patients présentant des arythmies héréditaires. Les protéines de ces complexes qui interagissent avec Na\textsubscript{v}1.5 peuvent être classées en 1) protéines d’ancrage ou adaptatrices ; 2) enzymes qui se lient et modifient Na\textsubscript{v}1.5 ; et 3) protéines qui régulent les propriétés biophysiques du canal.

Ces récents résultats illustrent le fait que la régulation de l’expression, la localisation cellulaire et l’activité de Na\textsubscript{v}1.5 sont finement régulées par des mécanismes moléculaires complexes qui, à l’heure actuelle, ne sont que partiellement compris.

INTRODUCTION

The electrical activity of the heart is the result of the coordinated action of many cardiac ion transporters expressed at the membrane of the cardiomyocytes. Among them is the cardiac voltage-gated Na\textsuperscript{+} channel Na\textsubscript{v}1.5, which plays a central role under normal and pathological conditions. Na\textsubscript{v}1.5 initiates the cardiac action potential (AP), is essential for conduction of the AP, and contributes to its duration [1]. During the past decade, the central role of Na\textsubscript{v}1.5 in cardiac diseases has been revealed by the discovery of more than 150 naturally-occurring mutations in SCN5A, the gene encoding Na\textsubscript{v}1.5. These mutations...
have been linked to congenital and drug-acquired long QT syndromes (LQTS), Brugada syndrome (BrS), progressive conduction defects (such as the Lenègre-Lev disease), sudden infant death syndrome (SIDS) [2], and dilated cardiomyopathy [3, 4].

Nav1.5 is a glycosylated membrane protein consisting of 2015 or 2016 amino acids (depending on the splice variant) with an apparent molecular weight of about 220 kDa. The channel has four homologous domains (DI to DIV, fig. 1) each with six transmembrane segments (S1 to S6, fig. 1). The three interdomain linker loops and both the N- and C-termini of the channel are cytoplasmic. The S4 transmembrane segments have several charged residues that are involved in the activation of the channel (fig. 1, in green). A cluster of three hydrophobic amino acids (isoleucine-phenylalanine-methionine, IFM) in the III-IV linker is involved in fast inactivation (fig. 1, in red). The cardiac Na+ channel is known to associate with so-called β-subunits (~30-35 kDa, β1 to β4-subunits). For reasons of space limitation, the roles of the β-subunits will not be addressed in this short review. A recent excellent review of the β-subunits is detailed in Meadows and Isom [5]. The cellular distribution of Na1.5 in cardiomyocytes is still debated. A fraction of Na1.5 is located at the specialized cellular junctions known as the intercalated disks [6, 7], in close proximity to the gap-junctions formed by the connexin proteins. Furthermore, the localization of Na1.5 in lateral membranes and t-tubules has been reported in some, but not all studies [7, 8-10].

Many recent reports have provided evidence that Na1.5 is part of multiple multi-protein complexes located in different membrane compartments of the cardiac cells. Interestingly, in some instances the genes coding for these regulatory proteins were also found to be mutated in patients with inherited forms of cardiac arrhythmias [10-13].

FIG. 1 – La topologie membranaire de la sous unité α de Na1.5 est montrée, DI-DIV représentent les quatre domaines homologues de la sous unité α ; les segments 5 et 6 correspondent aux pores et les hélices S4 (en vert) servent de détecteurs de voltage. Les résidus IFM (isoleucine-phenylalanine-methionine) (encadré rouge) sont des acides aminés clés pour la porte d’inactivation rapide. Les neuf protéines qui interagissent avec Na1.5 sont montrées schématiquement avec leurs sites de liaison approximatifs. Pour deux d’entre elles (voir points d’interrogation), une interaction a été montrée par les essais de co-immuno-précipitation, mais les sites de liaison sont toujours inconnus.

FIG. 1 – Schematic representation of the α-subunit of Na1.5 and interacting proteins. The predicted membrane topology of the α-subunit of Na1.5 is illustrated. DI-DIV indicate the four homologous domains of the α-subunit; segments 5 and 6 are the pore-lining segments and the S4 helices (green) serve as voltage sensors. The IFM (isoleucine-phenylalanine-methionine) residues (red box) are key amino acids for fast inactivation gating. The nine proteins reported to interact with Na1.5 are represented schematically with their approximate binding sites. For two of them (with question marks), interaction has been only shown by co-immunoprecipitation experiments, but the binding sites are still unknown.
In this brief review article, we will focus on the proteins that have been shown to directly interact with Na\textsubscript{v}1.5 and discuss their function in normal physiological conditions as well as in pathological conditions. These proteins can be classified as 1) anchoring/adaptor proteins, 2) enzymes interacting with and modifying the channel, and 3) proteins modulating the biophysical properties of Na\textsubscript{v}1.5 upon binding (Table I). Several recent observations indicate that the regulation of the expression level, cellular localization, and activity of Na\textsubscript{v}1.5 is finely regulated by complex molecular mechanisms that we are only starting to elucidate.

**ANCHORING AND ADAPTOR PROTEINS**

**Ankyrin proteins**

In the human genome, three distinct genes (ANK1-3) code for ankyrin proteins. These proteins organize, transport, and anchor ion transporters to the actin and spectrin cytoskeleton [14]. Expression of ankyrin-B (ANK2) and ankyrin-G (ANK3) has been demonstrated in the heart [14]; and mutations in both genes have been reported to cause different types of cardiac arrhythmias. Genetic variants of ANK2 have been linked to diverse pathologic phenotypes such as LQTS type 4 [15], drug-induced LQTS, and sudden cardiac death, thereby defining an “ankyrin-B cardiac syndrome” [16]. Thus far, there is no evidence to suggest that Na\textsubscript{v}1.5 is directly regulated by ankyrin-B, even though cardiac Na\textsuperscript{+} channels, in ankyrin-B knock-out mouse myocytes, display late openings similar to the ones seen in Na\textsubscript{v}1.5 LQTS type 3 mutant channels [17]. In contrast, ankyrin-G was reported to directly interact with an ankyrin-binding motif of the linker loop between domain II and III [18] (Table I). Illustrating the physiologic relevance of this interaction, Mohler and co-workers described a BrS patient with a SCN5A mutation in this motif (E1053K) abrogating the interaction between Na\textsubscript{v}1.5 and ankyrin-B [10]. Using lentiviral vectors, this group [10] was able to express and follow the expression of wild-type and mutant Na\textsubscript{v}1.5 channels in adult rat myocytes. Wild-type Na\textsubscript{v}1.5 channels were correctly routed to the intercalated disks and lateral membranes, whereas E1053K channels remained in the cytoplasm of the infected myocytes [10]. The authors proposed that ankyrin-G may not only act as an anchoring protein for Na\textsubscript{v}1.5, but that the trafficking and sorting of the channel also depend on ankyrin-G. Further experiments are required to develop a comprehensive understanding of this interaction.

**Syntrophin proteins and dystrophin**

Na\textsubscript{v}1.5 has been reported to be part of the dystrophin multi-protein complex [19]. In a recent study [20], our group demonstrated that Na\textsubscript{v}1.5 is interacting with dystrophin via adaptor proteins called syntrophins. This interaction depends on the C-terminal PDZ domain-binding motif of Na\textsubscript{v}1.5 [21] (fig. 1) which is composed of the last three residues of the protein, serine-isoleucine-valine (SIV, Table I). In mice lacking dystrophin expression due to a loss-of-function mutation, similar to Duchenne muscular dystrophy in human patients, the protein level of Na\textsubscript{v}1.5 was decreased in cardiac tissue [20]. This lowered expression of the Na\textsuperscript{+} channel lead to reduced cellular Na\textsuperscript{+} current and conduction defects which were reflected on the mouse ECG by a prolongation of the QRS complex duration. The reduced expression of Na\textsubscript{v}1.5 protein could not be explained by a decrease of the SCN5A mRNA level [20], suggesting that either there is a defect of the translation process, or that a lack of dystrophin reduces the

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**Table I — Summarizing the nine proteins that have been reported to interact and regulate Na\textsubscript{v}1.5.**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Type of protein</th>
<th>Main effects on Na\textsubscript{v}1.5</th>
<th>Motif on Na\textsubscript{v}1.5</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankyrin proteins</td>
<td>anchoring-adaptor</td>
<td>Trafficking to the cell membrane</td>
<td>VPIAxxSD motif in loop II-III</td>
<td>[10,18]</td>
</tr>
<tr>
<td>Syntrophin proteins</td>
<td>anchoring-adaptor</td>
<td>Adapt to dystrophin complex and stabilization</td>
<td>PDZ-domain binding motif in C-terminus</td>
<td>[19,20,62]</td>
</tr>
<tr>
<td>Nedd4-like enzymes</td>
<td>Enzyme</td>
<td>Ubiquitylation and internalization</td>
<td>PY-motif in C-terminus</td>
<td>[29,34]</td>
</tr>
<tr>
<td>Calmodulin kinase II (\alpha)</td>
<td>enzyme</td>
<td>Phosphorylation (site unknown) and modulation of biophysical activity</td>
<td>Not determined</td>
<td>[38]</td>
</tr>
<tr>
<td>Protein-tyrosine-phosphatase-H1</td>
<td>enzyme</td>
<td>Phosphorylation (site unknown) and modulation of biophysical activity</td>
<td>PDZ-domain binding motif in C-terminus</td>
<td>[42]</td>
</tr>
<tr>
<td>14-3-3(\alpha)</td>
<td>alteration of biophysical properties</td>
<td>Modulation of steady-state inactivation</td>
<td>Loop I-II</td>
<td>[44]</td>
</tr>
<tr>
<td>Caveolin-3</td>
<td>alteration of biophysical properties</td>
<td>Mutant of caveolin-3 induce persistent current</td>
<td>Not determined</td>
<td>[11,12]</td>
</tr>
<tr>
<td>FHFH1B</td>
<td>alteration of biophysical properties</td>
<td>Modulation of steady-state inactivation</td>
<td>amino acids 1773-1832 in C-terminus</td>
<td>[50]</td>
</tr>
<tr>
<td>Calmodulin</td>
<td>alteration of biophysical properties</td>
<td>Many discrepant effects</td>
<td>IQ-motif in C-terminus</td>
<td>[55-59]</td>
</tr>
</tbody>
</table>
stability of the Na_1.5 protein. Ongoing experiments performed in our group should provide information regarding these two possibilities. In relation to their clinical relevance, these results may partially explain some of the conduction defects seen in Duchenne and Becker muscular dystrophy patients [22]. Since it has been reported that dystrophin is most likely excluded from the intercalated disks of human [23], rat [24], and mouse (Gavillet and Abriel, not published) cardiomyocytes, where Na_1.5 channel is clearly present [7], it can be postulated that Na_1.5 channels is found in at least two distinct pools. One pool, localized at the lateral membranes, may belong to the dystrophin complex, whereas another pool could reside at the intercalated disks. Interestingly, in a recent study from Boyden's group [9], it has been shown that dog cardiomyocytes isolated from scarred tissue five days after myocardial infarction displayed a reduced Na^+ current density, associated with a significant loss of Na_1.5 staining in the lateral membranes. However, at the intercalated disks Na_1.5 staining was clearly preserved. It may be that this lateral dystrophin-dependent pool of Na_1.5 is more sensitive to specific pathological insults than the intercalated-disk pool. This is an open question that merits further investigation.

ENZYMES INTERACTING WITH AND MODIFYING NA_1.5

Ubiquitin-protein ligases of the Nedd4/Nedd4-like family

Ubiquitin is a small protein of 76 amino acids found in all animal cells [25]. The covalent binding of ubiquitin moieties (i.e. ubiquitylation) to membrane proteins is a general mechanism involved in trafficking and/or internalization. Once ubiquitylated, internalized membrane proteins can be targeted to lysosomal or proteasomal degradation. Alternatively, they can also be deubiquitylated by specific proteases and recycled back to the membrane [26, 27]. Ubiquitylation of target proteins is performed by ubiquitin-protein ligases dubbed E3s [25]. Members of the Nedd4-like family of E3 ubiquitin-protein ligases are known to bind specifically to target proteins which have consensus domains known as PY motifs, with the sequence [UP]PxY [28]. Such PY motifs are found in the C-termini of all voltage-gated Na^+ channels with the exception of Na_1.4, Na_1.9 and Na_x [29,30], as well as in other ion channels [27, 31]. Nedd4/Nedd4-like enzymes have two to four WW domains [32] that can interact with these PY motifs. When expressed in Xenopus oocytes, Na_1.5 mediated INa has been shown to be decreased by Xenopus Nedd4 (homolog to human Nedd4-2) ubiquitylation [33]. Our group has recently attempted to address the molecular determinants of this regulation [34], and reported that the ubiquitin-protein ligase Nedd4-2 directly binds to the PY motif of Na_1.5 and ubiquitylates the channel in mammalian cells. In addition, a fraction of ubiquitylated Na_1.5 was found to be present in cardiac tissue, suggesting that membrane turnover/stability of Na_1 channels can be regulated in vivo via ubiquitylation. These results were confirmed and extended to other Na isoforms containing a similar PY motif [29, 30]. Importantly, Rougier and co-workers showed that Nedd4-2 increases the internalization rate of Na_1.5 channels expressed in HEK293 cells [29]. The human genome contains nine of such Nedd4-like E3 enzymes [35], and we recently showed that at least 8 of them are expressed at the RNA level in human cardiac tissue [31]. However, it remains unknown which of these Nedd4/Nedd4-like proteins is regulating Na_1.5 in a physiologic context and whether the PY motif may play a role in cardiac diseases. Experiments addressing these questions are currently being performed in our group.

Ca^{2+}/calmodulin-dependent protein kinase II

Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is a serine/threonine protein kinase that is expressed in many tissues, and that is known to transduce intracellular Ca^{2+} increase into phosphorylation of multiple proteins, including cardiac ion channels [36]. The clinical relevance of CaMKIIδc, a cardiac isoform of CaMKII, is illustrated by the fact this enzyme is up-regulated in human and animal heart failure models (see [37] for a review). In a recent work [38], phosphorylation and regulation of Na_1.5 by CaMKII has been reported by performing in vitro and in vivo experiments. The authors showed that CaMKIIδc is co-localized and can be co-immunoprecipitated with Na_1.5 in cardiac tissue [38]. However, thus far the site of interaction with Nav1.5 has not been elucidated. Over-expression of the CaMKIIδc enzyme in rabbit myocytes and in transgenic mice induced a Ca^{2+}-dependent shift of the steady-state inactivation curve towards negative voltages, slowed the recovery from inactivation, and markedly increased the persistent current. Congenital LQTS type 3 is caused by similar mutation-induced persistent currents in most cases [39]. During tachycardia, these biophysical alterations would decrease the availability of Na^+ current, while during bradycardia the persistent current-dependent prolongation of repolarization would be predominant. In vivo, the over-expression of CaMKIIδc in transgenic mice led to heart failure and episodes of ventricular tachycardia. However, it is unclear whether these arrhythmias are the direct consequence of the Na_1.5 biophysical alterations or other heart failure-related mechanisms.

Proteins tyrosine phosphatase PTPH1

The function of many ion channels is known to be modulated by their level of tyrosine phosphorylation, which depends on the antagonistic activity of protein tyrosine kinases and phosphatases [40]. Ahern and co-workers [41] recently showed that the protein tyrosine kinase Fyn, when over-expressed in HEK293 cells, modulated several biophysical properties of Na_1.5. In addition, it was proposed that Tyr-1495 of Na_1.5 was most likely phosphorylated by this tyrosine kinase. This residue is close the Ile-Phe-Met motif of the intra-
cellular loop linking domains III-IV (fig.1). Importantly, tyrosine phosphorylation of native cardiac Na$_{\text{v}}$1.5 could also be demonstrated [41]. In HEK293 cells, Fyn co-expression mainly shifted the availability curve (steady-state inactivation curve) toward depolarized potentials, and accelerated the recovery from inactivation of Na$_{\text{v}}$1.5 [41]. However, the site of interaction of Fyn with Na$_{\text{v}}$1.5 was not investigated. In a recent work from our group [42], we reported that the protein tyrosine phosphatase PTPH1 (also called PTPN3) interacts with the same PDZ-domain binding motif of Na$_{\text{v}}$1.5 as described for syntrophin proteins (see above). PTPH1 co-expression in HEK293 cells shifted the availability curve of wild-type Na$_{\text{v}}$1.5 toward hyperpolarized potentials, whereas this effect was abrogated when the PDZ-domain binding motif was mutated. These results suggest that tyrosine phosphorylation of Na$_{\text{v}}$1.5 modulates the stability of the inactivated state, and that this is the result of the balance between protein tyrosine kinase and phosphatase activities in cardiac cells. Whether PTPH1 targets the tyrosine that is probably phosphorylated by the tyrosine kinase Fyn [41] remains to be investigated. Finally, the role of this tyrosine phosphorylation of Na$_{\text{v}}$1.5 under physiologic or pathologic conditions has not yet been determined.

INTERACTING PROTEINS MODIFYING THE BIOPHYSICAL PROPERTIES OF Na$_{\text{v}}$1.5

14-3-3$\eta$ protein

The 14-3-3 proteins are dimeric cytosolic adaptor proteins found in all mammalian cells; among many other functions, these proteins bind to and regulate the trafficking of membrane proteins [43]. By performing yeast two-hybrid and co-immunoprecipitation experiments, Aloulis and co-workers [44] recently demonstrated that 14-3-3$\eta$ interacts with the N-terminal portion of the intracellular loop linking domains I to II (fig. 1, Table I). Furthermore, distinct co-localization with Na$_{\text{v}}$1.5 at the intercalated disks was reported. Co-expression of 14-3-3$\eta$ in COS cells did not modify the Na$_{\text{v}}$1.5-mediated peak current, but negatively shifted the inactivation curve and delayed recovery from inactivation, illustrating that 14-3-3$\eta$ proteins are able to modify the biophysical properties of ion channels. Since different isoforms of 14-3-3 proteins are expressed in cardiac cells [44], their specific roles in normal heart function, including the regulation of ion channels, require further investigation.

Caveolin-3

The gene encoding caveolin-3, CAV3, has recently been found to be mutated in patients with congenital LQTS [12] (LQTS type 9) and SIDS [11]. Caveolin proteins are important elements of plasma membrane invaginations called caveolae, in which there is an enrichment of signaling molecules and ion channels [45]. Caveolin-3, the cardiac muscle isoform, has previously been shown to co-immunoprecipitate with Na$_{\text{v}}$1.5 from rat cardiac tissue, a finding that was recently confirmed by Vatta and co-workers [12]. However, detailed information about how and where caveolin-3 interacts with Na$_{\text{v}}$1.5 is lacking (fig. 1). These proteins are co-localized in cardiac cells [12, 46, 47]. Interestingly, dystrophin is also a component of caveolae [48], which raises the possibility that the interaction of Na$_{\text{v}}$1.5 could be indirect via proteins of the dystrophin multi-protein complex. The role of the Na$_{\text{v}}$1.5/caveolin-3 interaction is not well understood. It has been reported that co-expression of Na$_{\text{v}}$1.5 with the mutated form of caveolin-3 found in LQTS and SIDS patients increased the persistent late current in HEK293 cells [11, 12], consistent with the phenotype (i.e. prolonged QT interval) of the patients. On the other hand, in rat cardiac myocytes, a rapid increase of Na$^+$ current in response to $\beta$-adrenergic stimulation by isoproterenol, which is PKA-independent because in presence of a PKA inhibitor, was completely abolished by anti-caveolin 3 antibodies [47]. Despite these interesting findings, the physiologic roles of these caveolar Na$_{\text{v}}$1.5 channels remain unclear.

Fibroblast Growth Factor Homologous Factor 1B (FHF1B) or FGF12-1b

The protein FHF1B (also named FGF12-1b), which belongs to the FGF family of growth factors, is known to be expressed in cardiac tissue [49]. However, in contrary to FGF proteins, FHF1B remains located intracellularly. Liu and co-workers [50] reported that FHF1B interacts with the proximal portion of the C-terminus of Na$_{\text{v}}$1.5 (fig. 1). In HEK293 cells, co-expression of FHF1B with Na$_{\text{v}}$1.5 shifted the steady-state inactivation relationship toward hyperpolarized values, without affecting the other parameters studied [50]. Interestingly, several LQTS type 3 and BrS mutations are located in the domain interacting with FHF1B (Table I). The SCNSA mutation D1790G [51] disrupted the binding of this protein with Na$_{\text{v}}$1.5 and abolished the FHF1B-induced shift of the steady-state inactivation. It has been proposed that this protein may act as a scaffold to adapt protein kinases to the channel [50]. However, the precise role of this protein in Na$_{\text{v}}$1.5 function and regulation should be studied in more detail. In addition, another member of the FGF family, FGF14-1b, has been shown to associate with Na$_{\text{v}}$1.5 [52], and down-regulate its activity. However the significance of this interaction seems to be restricted to the central nervous system since this regulatory protein is expressed in the brain, but not in the heart [52].

Calmodulin

Calmodulin (CaM) is a ubiquitous Ca$^{2+}$-binding protein that has been shown to be involved in many different cellular processes [53]. It is known that many ion channels use calmodulin as their constitutive or transient Ca$^{2+}$-sensing partner [54]; whereas Ca$^{2+}$ plays a central role in regulation of cardiac excitability and contraction [37]. The C-terminal domain of Na$_{\text{v}}$1.5 has a CaM-binding motif, called "IQ motif", with the
concordance sequence of IQxxxxRxxxxR (Table I). A similar IQ motif is also found in all eight Na+ isoforms [55]. Using different approaches, three studies [56-58] reported direct interaction of CaM with the IQ motif of Na,1.5. However, the functional consequences of this CaM-Na,1.5 interaction reported by these groups, and others [55, 59, 60], show many inconsistent results that are very difficult to reconcile. In many instances [56, 58-60], the voltage-dependence and stability of the inactivated state were found to depend on CaM and the IQ motif. However, the roles of Ca²⁺ and CaMKII in regulating the activity of Nav1.5, require further investigation. It has been postulated via CaM-dependent or independent pathways, clearly different cell types in which Nav1.5 was studied. The interested readers are referred to the article by Young and Caldwell [59] for an extensive discussion of this puzzling issue.

CONCLUSIONS AND PERSPECTIVES

In this brief review, we have summarized the known proteins that have been shown to directly interact with the cardiac Na⁺ channel Na,1.5. An important limitation to these findings is that many of these studies have been performed using “cellular expression systems”, e.g. mammalian cell lines or Xenopus oocytes, which do not fully recapitulate the cellular context of cardiac cells. Interestingly, we are now experiencing developments in this field by many groups, which are generating more physiologically relevant experimental approaches (for a review see [61]). Recently published studies have investigated genetically-modified mouse models and used sophisticated cell biology techniques applied to isolated cardiomyocytes to study Na,1.5 regulation [61]. In conclusion, based on the recent studies reviewed here, it is obvious that the regulation of the biosynthesis, trafficking, sorting, internalization, and degradation of Na,1.5 is far more complex than what may have been anticipated a few years ago. Furthermore, based on the long list of cardiac phenotypes found in patients with Na,1.5-related disorders, future studies will most likely allow us to decipher alternative roles of Na,1.5 in cardiac physiology and diseases.

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KEYWORDS: Channel Na,1.5, SCN5A, associated proteins, channelopathy.

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