The Cardiac Sodium Channel

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The upstroke phase of the cardiac action potential (AP) is mainly coordinated by cardiac sodium channels, which are immediately activated and generate a fast Na+ inward current, through the membrane, after membrane depolarization. In atrial and ventricular myocytes, the sodium current (INa) is principally governed by cardiac voltage-gated sodium channel 1.5 (Nav1.5) with a tinny contribution of NaV1.8. The human Nav1.5 channel is composed of a pore-forming α-subunit (227-kDa) and one or more auxiliary β-subunit (30-kDa).

cardiac sodium channel gene regulation

1. Introduction

The upstroke phase of the cardiac action potential (AP) is mainly coordinated by cardiac sodium channels, which are immediately activated and generate a fast Na^+ inward current, through the membrane, after membrane depolarization [1]. In atrial and ventricular myocytes, the sodium current (I_{Na}) is principally governed by cardiac voltage-gated sodium channel 1.5 ($Na_V1.5$) with a tinny contribution of $Na_V1.8$ [2]. The human $Na_V1.5$ channel is composed of a pore-forming α-subunit (227-kDa) and one or more auxiliary β-subunit (30-kDa) [3]. *SCN5A* gene with 80 kb length is located on chromosome 3p21 and consists of 28 exons which encode a protein of 2016 amino acid, the α-subunit of $Na_V1.5$ channel [4]. This protein contains four homologous sites (DI–DIV), each composed of six transmembrane segments organized into two functional modules. Segments from one to four (S1–S4) generate the voltage-sensing module (VS), and segments five and six (S5–S6) jointly with P-loop create the pore module (PM). Finally, an α-helical S4–S5 linker, whose function is to bind these two structures, the voltage-sensing and the pore modules. Moreover, there are intracellular linkers that are in charge of DI–DII, DII–DIII, and DIII–DIV binding, and more concretely, the DIII–DIV linker is the controller of pore closing, acting as a fast inactivation gate [5]. The VS and PM modules of the $Na_V1.5$ constitute preferred therapeutic targets for the treatment of several cardiac sodium channelopathies. Particularly, flecainide, as well as other class IC antiarrhythmic drugs, bind to the central cavity of the pore and block sodium permeation directly [5]. The class IA antiarrhythmic drugs (e.g., procainamide) and the class IB antiarrhythmic drugs (e.g., lidocaine) might act on a smaller surface of the central cavity of the pore as well [5]. However, polyunsaturated fatty acids (PUFAs) and PUFA analogs have been shown to be antiarrhythmic by inhibiting $Na_V1.5$ channel currents, probably through acting on the voltage-sensing S4 segments that control inactivation in these channels [6][7].

2. Genomic Regulation of the Cardiac Sodium Channel

2.1. Genetic Code of SCN5A

$Na_v1.5$ channel expression and function may be impaired due to variations in the genomic sequence of *SCN5A*, including missense, nonsense, splice-altering, and frame shift truncation [8][9]. These variations cause different cardiac diseases because of a loss- or gain-of-function and occasionally both, generating overlapped phenotypes [10]. For example, Brugada Syndrome (BrS) [10][11][12], progressive cardiac conduction disease (Lev-Lenegre disease) [13][14], and sick sinus syndrome [15][16] are some diseases caused by loss-of-function mutations in *SCN5A*. However, long QT syndrome type 3 (LQTS3) [10][17] and multifocal ectopic Purkinje-related premature contractions (MEPPC) [18][19][20] are due to gain-of-function mutations in *SCN5A*. Finally, a combination of gain- and loss-of-function mutations are associated with atrial fibrillation (AF) [21][22] and dilated cardiomyopathy (DCM) [20][22][23][24].

2.2. Regulation of SCN5A Transcription

2.2.1. Epigenetic Regulation of *SCN5A*

Regulation of *SCN5A* by Distinct Regulatory Elements and Histones

Gene transcriptional activation is not only modulated by transcription factors; in this process, the role of distinct regulatory elements (RE) is also important, as well as how these REs interact with chromatin, depending on DNA accessibility. Several authors have identified different roles of an enhancer cluster in the *SCN5A-SCN10A* locus, which modulate *SCN5A* gene expression [30][31][32]. RE-1 and RE-5 are located in an *SCN10A* and *SCN5A* intron, respectively, and RE-6, located downstream of *SCN5A*, contains genetic variants associated with PR intervals and QRS duration [30][31][33][34]. Moreover, Christoffels' lab [35] has recently demonstrated that there are several downstream *SCN5A* REs acting as cardiac-specific "super enhancers", concretely the intergenic region composed by RE6-9, which possess an extensive association with Histone H3 lysine (K) 27 acetylation (H3K27ac) [36]. RE6-9 has the ability to fine-tune *Scn5a-Scn10a* chromatin architecture modulating *Scn5a* expression. In addition, it has been identified that some single-nucleotide polymorphisms (SNPs) located in an enhancer region are able to regulate transcription factor binding and modulate gene expression. In particular, major alleles of rs6801957 and rs10428132 lead to *SCN5A* gene expression, while minor alleles cannot due to a loss of a T-box protein binding site [37][38]. Furthermore, an enrichment of H3K27ac and Histone H3 lysine (K) 4 trimethylation (H3K4me3) near of *SCN5A* promoter region in striated muscles regulates normal expression of *Scn5a* and improve the re-expression of *SCN5A* in denervated muscle [35][39][40]. Moreover, Lamin A/C (encoded by LMNA) is a component of the nuclear lamina, and its K219T mutation has been described to trigger a change in the distribution of the histone marks. Concretely, H3K9me and H3K27me, which are transcriptional repressive histone marks, and H3K4me3, which acts as transcriptional active histone mark, generate cardiac conduction defects through *SCN5A* inhibition and reduced I_{Na} density [41].

Regulation of *SCN5A* by Transcription Factors

During biosynthesis, *SCN5A* transcription is regulated by several transcription factors. Sometimes this transcription step can be enhanced or decreased, i.e., TBX5 has a binding site downstream of the *SCN5A* gene, and several authors have demonstrated that TBX5 knockout presents a decreased density of $Na_v1.5$ that leads to arrhythmias and eventually sudden cardiac death [42][43][44]. Additionally, GATA4 and GATA5 have their binding site in

the *SCN5A* promoter and intron 1 region. These transcription factors activate the *SCN5A* gene in human left ventricles, whereas heterozygous mutants for GATA4$^{+/-}$ show short PR intervals [45][46][47]. Moreover, MEF2C has its binding site in the *SCN5A* promoter region and enhances *SCN5A* transcription [48][49]. Finally, IRX3 gain-of-function upregulates *SCN5A* mRNA levels [50][51], whereas, on the contrary, FOXO1 and Snail negatively regulate *SCN5A* mRNA levels [52][53][54][55][56] (**Figure 1**).

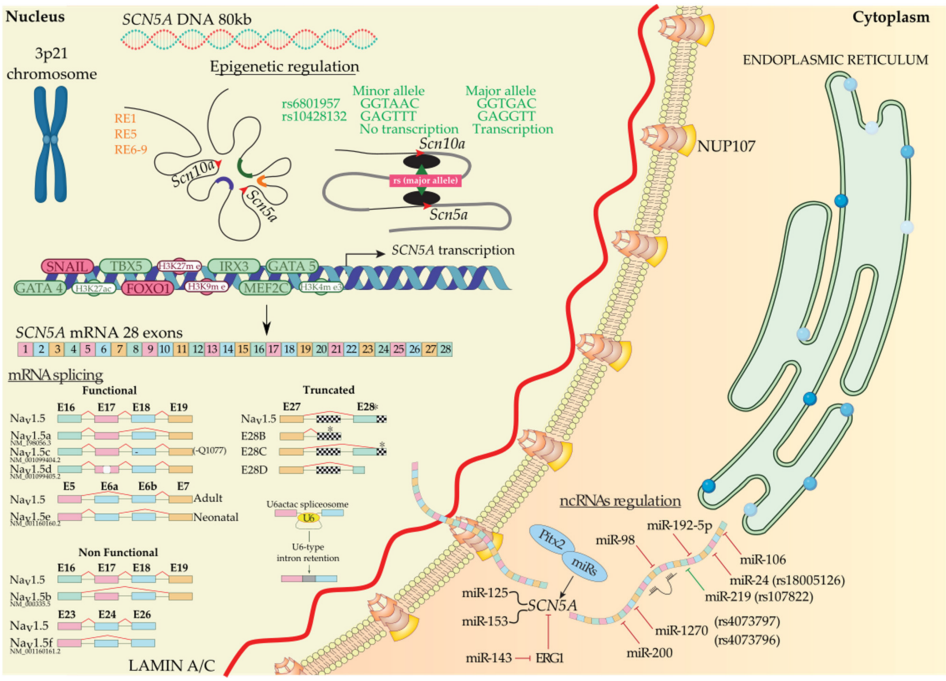

Figure 1. *SCN5A* biosynthesis: chromosomal localization, gene transcriptional activation modulated by regulatory elements, transcription factors, histones, and SNPs. Functional, non-functional, and truncated isoforms derived from mRNA splicing, mechanism of the U6-type intron retention, and post-transcriptional regulation mediated by ncRNAs. Alternative exon sequences, intronic or exonic sequences outside the open reading frame (squared), and stop codons (asterisks) are indicated.

2.2.2. Post-Transcriptional Regulation of *SCN5A*

Regulation of *SCN5A* by Alternative Splicing

After transcription, precursor mRNA copes with splicing and post-transcriptional modification to generate mature mRNA and finally translation into protein. Alternative splicing generate multiple functional ($Na_v1.5a$, $Na_v1.5d$, $Na_v1.5e$, and $Na_v1.5c$) and non-functional ($Na_v1.5b$, $Na_v1.5f$, and truncated) $Na_v1.5$ variants [57]. $Na_v1.5a$ isoform is characterized by the deletion of exon 18. This isoform is only present in small rodents and, compared with full-length $Na_v1.5$, leads to altered electrophysiological kinetics properties. There is no evidence of $Na_v1.5a$ expression in human cardiac cells [57][58]. Another alternative spliced variant of *SCN5A* generates $Na_v1.5c$ isoform, which has been identified as the most abundant isoform in humans. $Na_v1.5c$ is characterized by a 5′-trinucleotide deletion in exon 18, concretely a CAG—Glu (Q) in 1077 position, affected by the splicing machinery and generating a $Na_v1.5$ variant that contains 2015 polypeptides instead of 2016. It has been identified that the electrophysiological properties of $Na_v1.5$ and $Na_v1.5c$ are indistinguishable [58][59]. $Na_v1.5d$ is another $Na_v1.5$ variant, where 120 bp

fragment is deleted from exon 17. This $Na_v1.5d$ isoform is present in the fetal and adult human heart and has altered channel kinetics due to a reduction of open channel probability [58][60][61]. Finally, the last functional $Na_v1.5$ variant is $Na_v1.5e$ and is generated by alternative splicing on exon 6. It can be found $Na_v1.5e$ with 5′-exon 6 in neonatal (exon 6a) or 3′-exon 6 (exon 6b) in any adult mammalian heart [4][62]. $Na_v1.5e$ contains a K211 residue, instead of D211 residue in $Na_v1.5$, being responsible for slower kinetics of the channel [63]. $Na_vd1.5b$ is a non-functional $Na_v1.5$ variant and is generated by the deletion of exon 17 and exon 18. Heterologous expression reveals that exon 17 encodes an essential $Na_v1.5$ region that confers functionality to the channel [61][64]. This splice variant is present in mouse hearts, but there is no evidence of this variant in other mammals' hearts [61]. On the other hand, deletion of exon 24 of $Na_v1.5$ generates $Na_v1.5f$ variant; this isoform is highly detected in rat heart and human brain but not in the human heart [65][66]. Electrophysiological experiments evidenced that $Na_v1.5f$ is a non-functional variant [58]. Finally, it has been identified three C-terminal truncated spliced variants, E28B, E28C, and E28D, that generate reduced protein levels and no functional Na^+ currents in the normal fetal and adult human heart [67]. In another layer of complexity, in a very recent study, it has been evidenced that minor introns modulate gene families at a post-transcriptional level. Concretely, U6actac, which is a minor spliceosome component, modulates $Na_v1.5$ and $Ca_v1.2$ protein levels through the removal of minor introns in *Scn5a* and *Cacna1c*, regulating electrophysiological properties of cardiomyocytes [68].

3. Non-Genomic Regulation of the Cardiac Sodium Channel

Being an ion channel, $Na_v1.5$ is first synthesized as a primary protein chain that is subsequently folded in order to acquire the pore-forming three-dimensional conformation [57]. This tertiary structure is then assembled with its beta subunits, most likely (β1), and trafficked through the Golgi apparatus to be targeted to the corresponding cell membrane compartments [69]. Along this whole process, $Na_v1.5$ went through distinct non-genomic regulatory modifications and quality control steps conferring its unique conformational and functional identity as a voltage-gated sodium channel [57][70]. These steps are ensured by a growing set of regulatory proteins that have been demonstrated to covalently or non-covalently interact with $Na_v1.5$ [71]. In addition to the interacting proteins, $Na_v1.5$ function has been demonstrated to be influenced by wider intracellular (oxidative stress, metabolic stress, electrolyte homeostasis, etc.) and extracellular (pH, temperature, hormones, etc.) factors.

3.1. Regulation of $Na_v1.5$ Biosynthesis and Post-Translational Modifications

3.1.1. Regulation of $Na_v1.5$ Translation and ER Retention

The translation of $Na_v1.5$ starts in the cytosol and then pursue into the endoplasmic reticulum (ER). Anchoring the ribosome with the elongating $Na_v1.5$ polypeptide chain to the ER occurs when a signal peptide is recognized by the signal recognition particle (SRP) that targets the active ribosome to the rough endoplasmic reticulum (ER) membrane. Unlike cytosolic proteins, which have their signal peptide generally within the amino terminal, ion channels contain numerous signal sequences that are not restricted to the amino terminal [72]. Although the signal sequences of some ion channels such as Kv1.3 and CFTR have been already mapped to the second transmembrane spanning domain, almost 200 amino acids downstream from the NH_2 terminal [72], that of $Na_v1.5$

are not yet identified. Once anchored, the ribosome translocates the elongating polypeptide chain into the ER lumen [73]. As a transmembrane protein, the nascent $Na_v1.5$ is soon pushed to the ER membrane, where it is anchored and retained [73]. The ER retention is thought to occur when specific ER retention motifs embedded in the elongating $Na_v1.5$ polypeptide (most likely in the DI-DII linker of the sodium channel [74]) binds a cytosolic signal recognition particle (endoplasmic reticulum recognition particle, ERRP), that then directs the $Na_v1.5$-ERRP complex to receptors within the ER membrane [75][76][77]. The complex $Na_v1.5$-ERRP is then trapped within the ER, ensuring that the newly formed channel does not leave the ER membrane before finishing the folding and assembly steps [72]. At this level, several regulatory proteins and residues are reported to bind to this complex and facilitate the folding and maturation of the nascent protein [57][72][75][76][77][78][79][80] (**Figure 2**).

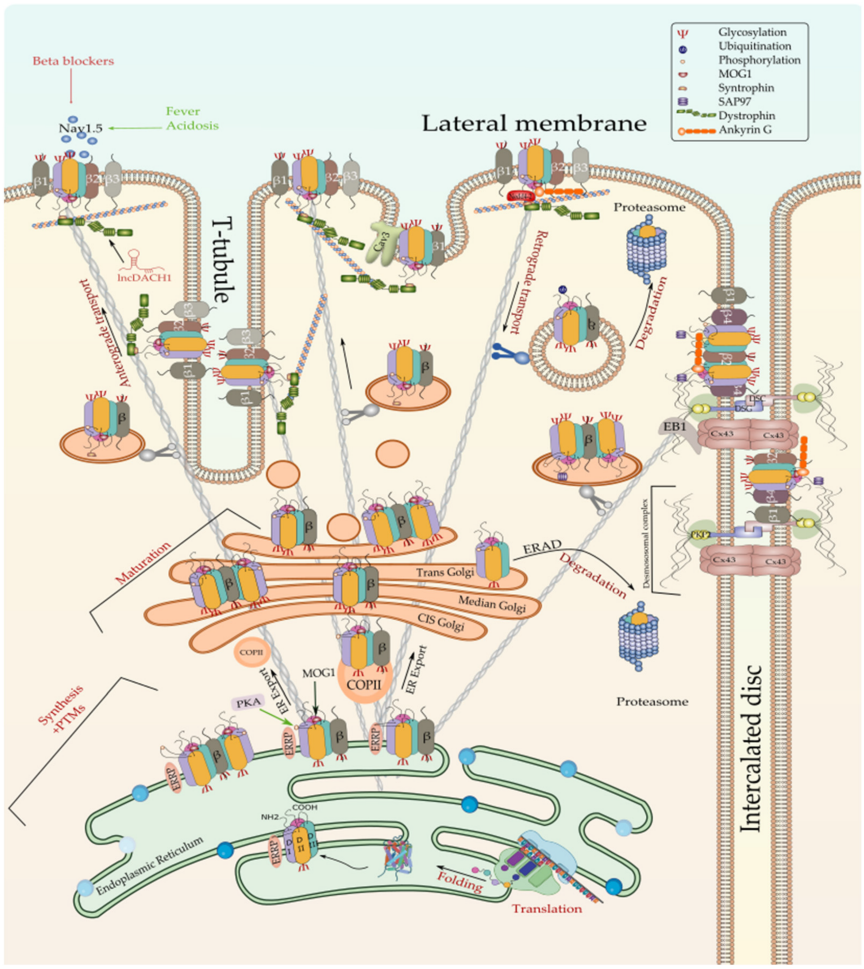

Figure 2. Biosynthesis and degradation pathways of $Na_v1.5$. Only one of the possible scenarios where $Na_v1.5$ assembles with one or more β-subunits early at the ER is depicted here. Furthermore, one possible scenario where ERAD-dependent degradation exclusively affects α subunit rather than α-β assembly is shown here since no information is currently available about the detailed process. ERRP—endoplasmic reticulum retention protein; β—beta subunit; PKA—protein kinase A; MOG1—RAN guanine nucleotide release factor; COPII—coat protein complex II; ERAD—ER-associated degradation; Cx43—connexin 43; PKP2—plakophilin 2; DSG—desmoglein; DSC—desmocollin; EB1—end-binding 1; Cav3—caveolin 3; PTMs—post-translational modifications.

The correct folding of the newly synthesized $Na_v1.5$ channels is commonly thought to be a condition for their forward trafficking to the cell membrane and their proper gating function. This notion has been tested by the exploration of $Na_v1.5$ trafficking-deficient mutants such as R282H, A124D, and V1378M that, due to folding defects, they failed to exit the ER and thus to reach the cell membrane [81][82]. Although the importance of this step in the life cycle of any ion channel, very scarce information is currently available about the mechanism of $Na_v1.5$ folding and its regulation. Nonetheless, it is currently established that one of the prerequisites for proper $Na_v1.5$ folding is core-glycosylation. In addition, molecular chaperone proteins such as protein disulfide isomerases (PDI), ER oxidoreductases (ERO), 70 kDa heat shock proteins (Hsp70), 90 kDa heat shock proteins (Hsp90), as well as calnexin and calreticulin, have been demonstrated to regulate the folding of the nascent proteins and the ER-associated degradation of the misfolded proteins [84][85][86][87][88].

Some antiarrhythmic drugs such as mexiletine, quinidine, and flecainide proved their efficiency rescuing the trafficking of some misfolded $Na_v1.5$ variants, thus playing the role of pharmacological chaperones [82][90]. In addition, curcumin, a major constituent of turmeric known to block the ER calcium pump, has also been reported as effective in rescuing the I_{Na} current of L325R misfolded $Na_v1.5$ channels [26]. Low temperature has also been demonstrated to trigger the rescue of misfolded $Na_v1.5$ mutants [90], probably through slowing the folding process, which prevents protein misfolding and aggregation [91].

3.1.2. Co-Translational and Post-Translational Regulation of $Na_v1.5$

N-Linked Glycosylation of Nascent $Na_v1.5$

One of the earliest modifications that the $Na_v1.5$ undergoes co-translationally once inserted into the ER is the N-glycosylation [69][83]. This quality control step has been first evidenced in the rat heart by Cohen and Levitt, who have found that glycosylation increases $Na_v1.5$ mass by only 5%, compared to 25–30% increases observed in other voltage-gated sodium channel isoforms [92]. Glycosylation initiates in the ER and terminates in the Golgi [83][93]. In the ER, glycosylation initiates when glycan (Glc3Man9GlcNAc2) is dissociated from a lipid derivative by oligosaccharyl transferase (OST) and bind to the amide nitrogen of asparagine (N) localized in the extracellular side of the nascent $Na_v1.5$ protein [70][94]. Although no validated “map” of the N-glycosylation sites has been published yet for $Na_v1.5$, 13 potential external N-glycosylation sites have been identified in human $Na_v1.5$ [95], and at least 14 putative N-linked glycosylation sites have been reported in the rat cardiac sodium channel [92]. The N-glycosylation of the newly formed cardiac sodium channel has been reported to be a prerequisite for proper $Na_v1.5$ folding and subsequent surface expression as well as an assembly with its β subunits [69][83][96]. According to Arakel et al., $Na_v1.5$ maturation strongly depends on the presence of the auxiliary β1 that binds to the pore-forming α subunit and promotes its glycosylation and its trafficking to the cell membrane [97].

In this context, N-glycosylated $Na_v1.5$ is thought to undergo subsequent serial de-glucosylation steps and extreme quality controls involving the ER-resident chaperones, which will ensure that only correctly folded and fully glycosylated channels can be trafficked [83][93][98]. Interestingly, Mercier et al. found that early N-glycosylated $Na_v1.5$ channels generated in the ER could reach the cell membrane through an unconventional trafficking pathway bypassing the Golgi stacks while functional channels are trafficked through the conventional pathway that

is Golgi-dependent [83]. In addition, ER-resident chaperones such as Calnexin and Calreticulin have been reported to play a crucial role in controlling ion channels folding and efficient export to the Golgi [99][100][101]. However, there is no evidence of physical interaction of Calnexin and $Na_v1.5$ despite their proven co-localization in the ER [102][103]. While properly folded $Na_v1.5$ are trafficked forward to the cis-Golgi where they will be fully maturated, misfolded $Na_v1.5$ are retained in the ER to be later degraded, most likely through the activation of the unfolded protein response (UPR) pathway and/or ER-associated degradation (ERAD) pathway that is linked to the cytoplasmic ubiquitin-proteasome pathway [104][105][106].

Phosphorylation and Dephosphorylation of $Na_v1.5$

In addition to N-linked glycosylation, $Na_v1.5$ undergoes phosphorylation as a post-translational modification [107]. Thirty years ago, Shubert et al. brought the first evidence of $Na_v1.5$ phosphorylation by protein kinase A (PKA) through the activation of the β-adrenergic system by isoproterenol, which led to an increased level of cAMP, which in turn reduced Na^+ current (I_{Na}) [108]. These findings were further confirmed by a subsequent study by Frohnwieser and his co-worker, who showed that combined cytosolic injection of cAMP and a PKA activator increased I_{Na} suggesting a modulatory effect of PKA on human $Na_v1.5$ [109]. The same study demonstrated that this modulatory effect of PKA is conferred by the DI–DII intracellular linker of $Na_v1.5$. In this regard, it has been reported that the rat $Na_v1.5$ protein sequence harbors two distinct sites for PKA phosphorylation that were mapped to serine positions S526 (525 in human) and S529 (528 in human) [70][110][111][112]. These sites are localized in the cytosolic loop interconnecting DI and DII of $Na_v1.5$, where the three putative RXR-type (R479KR481, R533RR535, and R659QR661) ER retention motifs have been localized too [74][107][113]. Zhou et al. have previously demonstrated that PKA activation promotes trafficking of channels to the plasma membrane [113]. In the same context, Scott et al. have shown that a PKA-PKC mediated phosphorylation of NMDA receptor masks its ER retention motifs leading thus to its release from the ER and exportation to the cell membrane [114]. Taken together, these findings suggest a similar mechanism where the phosphorylation of $Na_v1.5$ at S525 and S528 by PKA leads to changes in the $Na_v1.5$ conformation that masks the ER retention signals and eases the trafficking of the channel to the cell membrane [112][115]. This is consistent with the idea that proper folding of $Na_v1.5$ unmasks its ER retention motifs and facilitates its forward trafficking to the Golgi apparatus [76].

In an antagonistic way to PKA, $Na_v1.5$ is downregulated by protein kinase C (PKC)-mediated phosphorylation which leads to a reduced channel density at the cell surface and I_{Na} decay [116]. Although ten different PKC isoforms have been identified in human ventricular myocytes and in different animal species [117], isoform-specific activation/inhibition studies suggested εPKC isoform as the key player in the PKC-mediated regulation of $Na_v1.5$ and I_{Na} [118][119]. Nonetheless, PKCδ-mediated $Na_v1.5$/I_{Na} downregulation either directly through phosphorylation at S1503 or indirectly through elevated mitoROS production has been reported [120]. In addition, a minor role of αPKC reducing I_{Na} through angiotensin II has also been described [121]. As a direct mechanism, the PKC (particularly εPKC) effect on $Na_v1.5$ and I_{Na} has been partially attributed to the phosphorylation of a conserved serine S1503 of the DIII-DIV cytosolic linker of $Na_v1.5$ [122][123]. However, intracellular metabolic changes have been described as a mediator of PKC activation and PKC-mediated phosphorylation of $Na_v1.5$ [120]. In this regard, high intracellular levels of NADH have been described as triggers of PKC, thus leading to overproduction of mitochondrial reactive oxygen species (mitoROS) and I_{Na} decay [124][125][126]. This effect has been demonstrated to be mediated by

glycerol 3-phosphate dehydrogenase 1 (GPD1L) [127] and could be reversed by NAD^+-mediated PKA activation [124][128][129][130]. Interestingly, Fouda et al. have demonstrated that PKA and PKC phosphorylation pathways could be activated by Cannabidiol and Estradiol and that this activation could rescue the high glucose-induced changes in $Na_v1.5$ properties [131][132].

Importantly, not far from the PKA phosphorylation sites in $Na_v1.5$ DI–DII linker, there is a Ca^{2+}/Calmodulin-dependent Protein Kinase II (CaMKII) phosphorylation site as well, which was mapped to S516 [133]. This CaMKII phosphorylation site is not the only one in $Na_v1.5$ since Ashpole et al. have identified four extra potential sites; all of them are localized in DI–DII linker, suggesting linker I as a hotspot for $Na_v1.5$ phosphorylation [133]. However, a recent study by Herren et al. identified 23 sites along $Na_v1.5$ intracellular regions that could be phosphorylated by CaMKII in human $Na_v1.5$ [134]. More recently, Burel et al. identified two further CaMKII phosphorylation sites localized in the C-terminal region of $Na_v1.5$ [135]. Several studies have shown that $Na_v1.5$ is regulated by CaMKII and that activation of this kinase increases the so-called pathogenic late cardiac sodium current I_{NaL} [136]. Interestingly, El Refaey et al. demonstrated that I_{NaL} could also be regulated by B56α, the key regulatory subunit of the PP (protein phosphatase) 2A holoenzyme [137]. This phosphatase is targeted by ankyrin-G to the $Na_v1.5$-CaMKII -βIV spectrin axis at the ID where it is thought to dephosphorylate $Na_v1.5$ at S571 in the DI-DII linker via B56α balancing, thus the CaMKII-dependent phosphorylation of the cardiac sodium channel. According to a study by Deschênes et al., inhibition of CaMKII slowed $Na_v1.5$ channel current decay, produced a depolarizing shift in fast inactivation, and slowed entry into inactivated states [138].

$Na_v1.5$ is also phosphorylated by Tyrosine kinases. In this regard, phosphorylation of $Na_v1.5$ by the Src family Tyrosine kinase Fyn has been first reported by Ahern and co-workers, who have demonstrated that this kinase acts by increasing the rates of recovery from fast-inactivated states, thus impairing the steady-state inactivation of $Na_v1.5$ [139]. Fyn kinase acts most likely on Tyr1495 of $Na_v1.5$ not far from the Ile-Phe-Met (IFM) motif of DIII–DIV linker that is known to modulate the rapid inactivation process of the channel [5]. In the heart, Fyn tyrosine kinases are reported to co-localize with $Na_v1.5$ channels at adherens junctions, where they modulate electrical coupling and propagation of action potential [140][141]. Iqbal et al. found that the major $Na_v1.5$ splice variants Q1077 and delQ1077 are differentially phosphorylated by Fyn kinase, which results in coordinated steady-state rapid inactivation kinetics for smooth electrical activity of the heart [142]. The same researchers suggested a multistep mechanism by which Fyn kinases bind and modulate $Na_v1.5$. This mechanism starts by the association of Fyn kinase to proline-rich regions in the DI–DII linker and C-terminal region of $Na_v1.5$, which activates the phosphorylation of neighboring tyrosine residues in the N-terminal region (Y68, Y87, and Y112), DIII–DIV linker (Y1494, Y1495), and C-terminal region (Y1811, Y1889) [139][142][143]. Particularly, Y1494 and Y1495 of the DIII–IV linker have been demonstrated to play an essential role in the anchoring of $Ca2^+$/Calmodulin to the $Na_v1.5$ inactivation gate, and thus Fyn-mediated phosphorylation of the two Tyrosine residues has been suggested to reduce or abolish calmodulin binding and to impair the interaction of the side chain with the inactivation gate receptor [144].

Arginine Methylation

Beltran-Alvarez and co-workers evidenced for the first time that $Na_v1.5$ is post-translationally modified by arginine methylation at three residues (R513, R526, and R680) within the $Na_v1.5$ DI–DII linker [146]. This modification is

catalyzed by arginine methyltransferases (PRMT) PRMT-3 and PMRT-5 and leads to an increased expression of $Na_v1.5$ in cell surface [147]. Studying the PTMs of $Na_v1.5$ in end-stage heart failure patients, the same team demonstrated that methylation of R526 is the major quality control step of any $Na_v1.5$ arginine or lysine residue [148].

N-Terminal and Lysine Acetylation

Another PTM during the $Na_v1.5$ life cycle is the acetylation process. Two types of acetylation have been reported so far: reversible and irreversible. The first type is mediated by histone acetyltransferases (HATs) which exert N-terminal acetylation of a $Na_v1.5$ lysine residue leading to enhanced trafficking of $Na_v1.5$ and therefore to an increased I_{Na} current [149], whereas the second type of acetylation is mediated by N-terminal acetyltransferases (NATs), where a $Na_v1.5$ alanine residue is acetylated and has been reported as a $Na_v1.5$ degradation signal [147]. Interestingly, native $Na_v1.5$ channels purified from end-stage heart failure patients were reported to lack the initiation of methionine and be acetylated at the resulting initial alanine residue [148]. Recently, Vikram et al. showed that $Na_v1.5$ undergoes reversible lysine acetylation. For instance, sirtuin 1 deacetylase (Sirt1), an NAD^+-dependent lysine deacetylase, has been demonstrated to regulate $Na_v1.5$ channels by deacetylating lysine residue 1479 (K1479) in the DIII–DIV linker, which promotes $Na_v1.5$ cell surface expression and increases I_{Na} [150]. Interestingly, the murine model of cardiac Sirt1 deficiency presents fatal cardiac conduction defects as a result of K1479 hyperacetylation, which decreases $Na_v1.5$ cell surface expression and reduces I_{Na}. These arrhythmogenic substrates are similar to those characterizing human $Na_v1.5$ loss-of-function cardiac arrhythmias suggesting that $Na_v1.5$ Sirt1-mediated deacetylation is crucial for the proper function of the cardiac sodium channel. It is noteworthy that the authors of this study raised an interesting point regarding the role of the functional interaction and interplay between different PTMs fine-tune regulating the $Na_v1.5$ channel expression and function. In this regard, it has been suggested that $Na_v1.5$ is regulated by Sirt1-mediated interaction between lysine acetylation and the ubiquitination in one hand and NAD^+ dependent interplay between PKC-mediated phosphorylation and Sirt1-mediated deacetylation in another hand [150].

SUMOylation

Although more than 25 years have passed since the discovery of SUMOylation, a post-translational modification conjugating a small ubiquitin-like modifier (SUMO) molecule to a lysine residue in the substrate protein [151], very scarce information are currently available about the regulation of $Na_v1.5$ by SUMOylation. For instance, only one study, that of Plant et al., has reported that one of the mechanisms underlying I_{NaL} elevation in response to acute cardiac hypoxia is the quick SUMOylation of $Na_v1.5$ channels at the cell surface [152]. Particularly, SUMOylation of K442 residue has been reported to contribute to the pathological increasing of I_{NaL} and action potential prolongation through activation of $Na_v1.5$ channels when they should normally be inactivated.

S-Nitrosylation

S-nitrosylation, a PTM consisting of the covalent binding of a nitrogen monoxide (NO) moiety to the thiol side chain of cysteine in the target protein, has recently gained progressive attention as a crucial quality control step that is required for the proper function of a given protein [153]. In the cardiomyocytes, NO is produced by neuronal nitric oxide synthase (nNOS) [154]. nNOS mediated S-nitrosylation of $Na_v1.5$ has been demonstrated to maintain I_{NaL} [155]. Interestingly, nNOS has been shown to interact with $Na_v1.5$ via its regulating protein α1-

syntrophin, which acts as a scaffolding protein bringing together $Na_v1.5$ with nNOS and plasma membrane Ca-ATPase (PMCA4b) (an inhibitor of nNOS activity) [156]. Therefore, LQTS-associated α1-syntrophin mutation has been demonstrated to break the SNTA1- PMCA4b association neutralizing, thus the nNOS inhibition and increasing $Na_v1.5$ S-nitrosylation, which in turn increase I_{NaL} currents [156]. A similar effect has been observed with a decreased caveolin 3(Cav3) expression, which has been shown to enhance S-nitrosylation of $Na_v1.5$ through increasing the nNOS activity, which increased I_{NaL} in cardiomyocytes [157]. However, a very recent study by Wang and co-workers suggested an indirect mechanism by which S-nitrosylation modulates the cardiac sodium channel expression and function. For instance, NO has been demonstrated to down-regulate *SCN5A* expression and $Na_v1.5$ function through S-nitrosylation of regulatory transcription factor FOXO1 [158].

Lipoxidation

Lipoxidation refers to the establishment of covalent adducts between reactive products of lipid peroxidation and macromolecules such as proteins, phospholipids, and DNA [159]. Recently, lipoxidation gained interest as a post-translational modification of the cardiac sodium channel that gives further evidence on the regulation of $Na_v1.5$ by oxidative stress [160]. Nonetheless, little information is currently available about the mechanism of $Na_v1.5$ regulation by lipoxidation. In this respect, in vitro data by Nakajima and co-worker provided the first evidence that $Na_v1.5$ is post-translationally modified by lipoxidation during oxidant injury and that sodium channel dysfunction evoked by lipid peroxidation could be prevented by scavenging Isoketals (IsoKs), which are the most reactive products of lipoxidation [161].

Methionine Oxidation

A previous study by Quiñonez et al. demonstrated that skeletal $Na_v1.4$ fast inactivation could be impaired by oxidizing at least two methionine residues in the channel [162]. These findings have been supported in cardiac $Na_v1.5$ as well, where oxidative modification of the methionine within the IFM motif has been shown to lead to a drastic loss of $Na_v1.5$ inactivation [163]. Interestingly, $Na_v1.5$ channels and I_{Na} currents have been reported to be indirectly modulated by CaMKII, the activation of which depends on the oxidation of its own methionine residues [164].

Palmitoylation

Palmitoylation (also called S-acylation) is the PTM of protein cysteines with saturated fatty acids that modify protein hydrophobicity and thereby influence their function [165]. Palmitoylation has been reported to regulate ion channel's function, most likely through controlling their trafficking and cell membrane expression [69][166]. An early study by Schmidt et al. showed that $Na_v1.5$ is subject to palmitoylation [69]. However, palmitoylation has been demonstrated to slightly influence cell surface expression of $Na_v1.5$ and rather significantly impact channel availability by regulating the voltage dependence of steady-state inactivation in both HEK293 cells and cardiomyocytes [167]. Additionally, cysteine residues predicted to be palmitoylated in $Na_v1.5$ are mapped to the DII–DIII linker of the channel by prediction algorithms [167].

3.1.3. Regulation of the ER-to-Golgi Trafficking

Well folded and assembled proteins are supposed to cross the ER-Golgi space in vesicle budding guided by cytoskeletal proteins [168]. Studying the subcellular distribution of the cardiac sodium channel $Na_v1.5$ in HEK293 Cells and canine cardiac myocytes, Zimmer et al. noticed an accumulation of the intracellular channels within the ER and a lower channel density in the Golgi apparatus. Thereby, they proposed that ER plays the role of an intracellular reservoir where sodium channels are transiently stored [169]. As discussed previously, stimulation of PKA likely results in the activation of the ER-to-Golgi trafficking, which in turn leads to a rapid increase of the channel density in the cell membrane [74]. However, the whole mechanisms underlying the ER exit of $Na_v1.5$ to the Golgi is not yet fully deciphered, and current advances in this topic show that not only the PKA-mediated phosphorylation of the $Na_v1.5$ ER retention sites is what facilitates its ER-Golgi exportation. That is, several proteins and enzymes have been reported to bind to $Na_v1.5$ once retained to the ER and enhance its release. In this context, Wu et al. have identified the Ran-guanine nucleotide release factor (RANGRF or MOG1) as a cofactor of $Na_v1.5$, which by binding to its intracellular loop DII–DIII facilitates its cell surface expression [170]. Using the DII–DIII linker of $Na_v1.5$, in yeast two-hybrid analyses, the team demonstrated that MOG1 is crucial for the optimal expression of $Na_v1.5$ and promotes its ER export and intracellular trafficking to the plasma membrane [170]. These findings are consistent with Chakrabarti et al. study, which showed that silencing of MOG1 expression by small interfering RNAs caused retention of $Na_v1.5$ in the ER, reduced $Na_v1.5$ plasma membrane expression, and disrupted the $Na_v1.5$ targeting to the cell surface, in particular, to the caveolin-enriched microdomains (caveolae) [171]. A subsequent mutational study performed by Yu et al. further revealed that mutations in the amino acids E83, D148, R150, and S151 of MOG1 disrupt its interaction with $Na_v1.5$ and significantly reduce the cardiac sodium channel trafficking to the cell surface, suggesting that these amino acids are important for the MOG1-$Na_v1.5$ binding and interaction [172]. The same team found that MOG1-mediated trafficking and function of $Na_v1.5$ requires the interaction of MOG1 with two small GTPases SAR1A and SAR1B and that the knockdown of both enzymes abolishes the function of MOG1 [173]. Furthermore, it has been demonstrated that activation of SAR1 leads to the recruitment and internalization of $Na_v1.5$ cargo into the coated transition vesicle COPII-coated vesicles that will ensure its ER-to-Golgi trafficking [173]. The $Na_v1.5$ ER export is also controlled by Dynamitin as demonstrated by Chatin et al., who have proved, using a yeast two-hybrid system, that Dynamitin (C-terminal domain), interacted with the $Na_v1.5$ DI–DII linker between amino acids 417 and 444 and that this interaction is crucial for the $Na_v1.5$ cell-surface density probably through controlling the ER-to-Golgi trafficking [174].

3.1.4. Regulation of $Na_v1.5$ Maturation and Golgi Export

Once in the Golgi, N-glycosylated $Na_v1.5$ undergoes additional mannose trimming and terminal glycosylation where acetyl-glucosamine, oligosaccharides, and finally sialic acid residues are sequentially added as the protein crosses the distinct Golgi cisternae. It has been demonstrated that glycosylation regulates voltage-gated sodium channels (including $Na_v1.5$) gating, inactivation, and recovery process during cardiac AP by interfering with the electric field near the gating sensors [175][176][177][178][179]. Hence, it has been suggested that extracellular sialic acid residues, which are negatively charged at physiological pH, modulate the sensitivity of the $Na_v1.5$ voltage sensor domains to the transmembrane electrical potential fluctuation [180]. Particularly, sialic acid residues localized to DI S5-S6 have been demonstrated to regulate the sialic acid-dependent gating of $Na_v1.5$ [95].

Mature $Na_v1.5$ (fully glycosylated) are exported from the Golgi apparatus, which acts as a major secretory sorting hub that targets newly synthesized proteins to their final subcellular destinations [181]. Although the current knowledge on the exact mechanisms regulating the $Na_v1.5$ export from the Golgi and trafficking to the cell membrane is still limited, a recent study by Ponce-Balbuena and co-workers reported that $Na_v1.5$ Golgi export is driven by a trafficking signal localized in its terminal COOH region. This signal corresponds to a binding site of the adaptor protein complex 1 (AP1) mapped to $Na_v1.5$'s Y1810 residue. AP1-marked $Na_v1.5$ will be then incorporated into clathrin-coated vesicles that will migrate to the cell membrane where the channel will be anchored [182]. The same team showed that the $Na_v1.5$ cross the Golgi-cell membrane space by a common anterograde trafficking pathway as Kir2.1. These findings support previous studies demonstrating that both ion channels form a channelosome that shares common trafficking, targeting, anchoring, recycling, and degradation pathways [183][184].

3.1.5. Regulation of the $Na_v1.5$ Targeting to the Cell Membrane

Over the last few years, it became widely accepted that not all the $Na_v1.5$ proteins synthesized in one cardiomyocyte undergo the same regulatory steps till reaching their final localization in the cell membrane [185]. After years of debate and controversial studies about the subcellular distribution of the cardiac sodium channel, the new cellular imaging techniques excluded the idea of an exclusive expression of $Na_v1.5$ at the ID [141][186] and gave way to a more conceivable model that suggests a multi-pool aggregation of $Na_v1.5$ along with the cellular membrane compartments including the LM and the T-tubules [187][188][189]. Being in one membrane domain or the other put the $Na_v1.5$ in distinct microenvironments composed of different interacting proteins that regulate its gating function and biophysical properties. Above all these interacting proteins, beta subunits are without doubt the ones that most gained interest in this field over the last few decades as their presence and function are dependent on the presence of the pore-forming α-subunit (**Figure 2** and **Figure 3**).

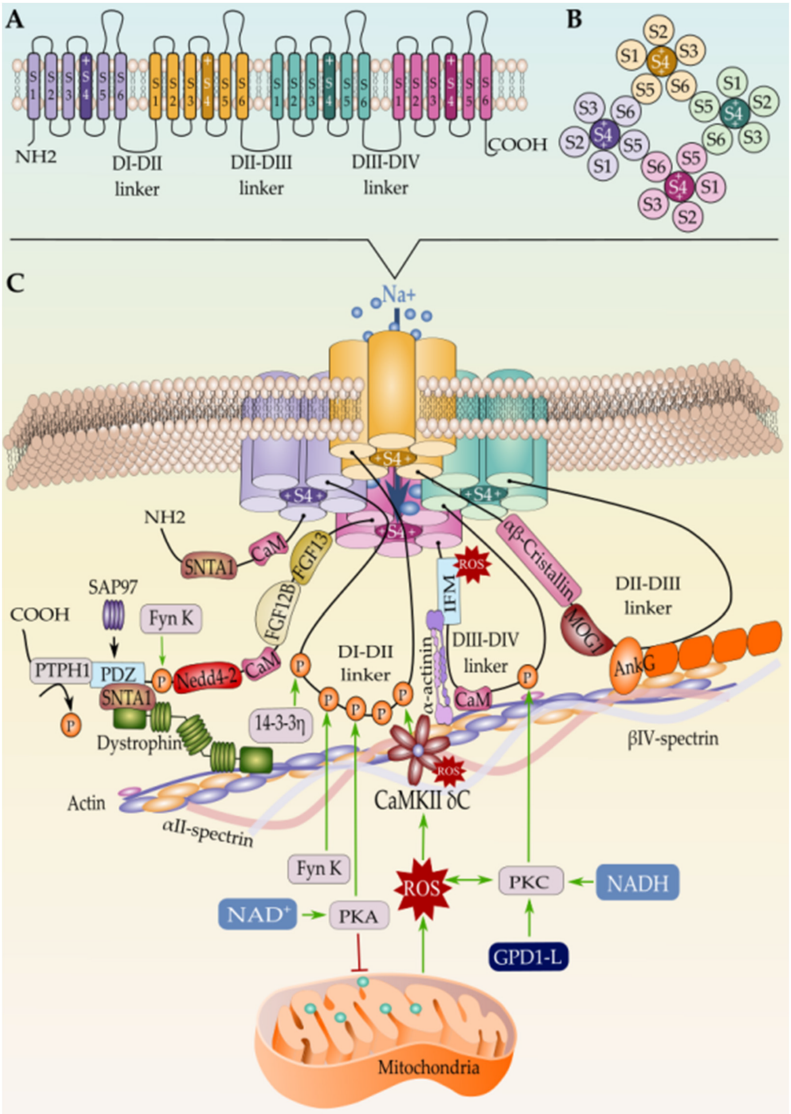

Figure 3. (**A**) Schematic representation of the $Na_v1.5$ secondary structure, (**B**) the intracellular view of the channel, and (**C**) the tertiary structure along with the interacting proteins. Only proteins with known binding sites in $Na_v1.5$ are represented here. Mechanism of $Na_v1.5$ regulation by the mitochondrial reactive oxygen species ROS is represented as well.

Regulation of $Na_v1.5$ by β-Subunits

The β subunit family consists of four different proteins β1–4 encoded by four genes, *SCN1B–SCN4B*, respectively, with β1 alternatively spliced into two isoforms, β1A and β1B [190]. The β-subunits, most likely β1-subunits, assemble with $Na_v1.5$ at the endoplasmic reticulum and influence its maturation and trafficking to the plasma membrane [97][191]. Alpha-beta subunits assembly is either covalent (β2 or β4) or non-covalent (β1 or β3) [192]. Particularly, β 4-$Na_v1.5$ covalent association is ensured by an extracellular cysteine–cysteine single disulfide bond [193][194], while β2 does not form a disulfide linkage at this position with $Na_v1.5$ as recently specified [5], whereas β1 and β3 non-covalently interact with $Na_v1.5$ through the channels DIV and DIII voltage gating domain respectively [195].

Despite the structural similarities between β2/β4 on one hand and β1/β3 on the other hand, their expression differs from one cellular sub-domain to another. Inside the cardiomyocyte, β3 are expressed at the T-tubules and β4 at the ID, while β1 and β2 are found at both locations [186][196][197]. Zimmer et al. have suggested that, unlike β2, β1 associates to $Na_v1.5$ early at the ER, and both α and β1 subunits are trafficked together to their final destination at the cell membrane [198]. Subsequent studies revealed that β1-subunits enhance the α-subunits dimerization and promote the dominant-negative effect of trafficking defective mutants [199]. β2 has been reported to promote surface localization of $Na_v1.5$ [200]. Importantly, β3 subunits have been demonstrated to bind to $Na_v1.5$ in multiple sites and promote the formation of α subunit oligomers, including trimers [201]. However, β4 has been reported as a modulator of $Na_v1.5$ kinetic and gating properties by increasing I_{Na} [202]. Taken together, these findings are consistent with the idea that the distinct sodium channel β subunits provide support for the pore-forming subunit, facilitate the trafficking of the mature channel to the different membrane domains, and modulate the gating function of $Na_v1.5$ by increasing the I_{Na} [203][204][205][206][207].

The $Na_v1.5$ and the Intercalated Disc Interactome

As suggested by the Delmar research team, several evidence point to the fact that the ID is not a hub of proteins playing independent functions within the cardiomyocyte, but rather a network of molecules interacting together in order to fulfill a specific function (AP propagation, cell-to-cell coupling, cardiac excitability, etc.) that cannot be accomplished if this “interactome” is impaired [208]. As a component of the ID proteins, $Na_v1.5$ has been demonstrated to be in the heart of this interactome by physically and functionally associating to several proteins belonging to this macromolecular complex.

In this context, it is currently well known that $Na_v1.5$ targeted to the ID are “tagged” with synapse-associated protein 97 (SAP97), a scaffolding MAGUK ((membrane-associated guanylate kinase) protein that is abundantly expressed in human and rat ventricular myocardium [209]. SAP97 has been introduced as the determinant of the $Na_v1.5$ ID pool as it plays an important role in targeting $Na_v1.5$ along with Kir2.1 to this cell membrane domain [209][210]. Both channels were structurally evidenced to co-assemble to SAP97 by their C-terminal domains [209][211]. For $Na_v1.5$, it is assumed that the last three amino-acids (serine–isoleucine–valine or SIV motif) of the C-terminal region form a PDZ (postsynaptic density protein (PSD95), Drosophila disc large tumor suppressor (Dlg1), and zonula occludens-1 protein (zo-1) domain binding motif) that interacts with the syntrophin–dystrophin complex at the cardiomyocyte LM and PDZ domains of SAP97 at the ID [189]. In the absence of the PDZ-domain-binding motif of $Na_v1.5$ or SAP97, $Na_v1.5$ expression at the cell surface decreased, thus leading to a reduction in the cardiac I_{Na} in vitro [212]. However, a subsequent study by the same team demonstrated that in vivo ablation of SAP97 did not change $Na_v1.5$ localization and function, but it did decrease the cardiac potassium currents [213]. The authors of these studies justified this discrepancy by the fact that SAP97 silencing in vitro is induced in adult cardiomyocytes while in vivo, it is a constitutive ablation present early in development, which may impact protein expression and interactions.

In addition, the $Na_v1.5$-SAP97-Kir2.1 complex has been demonstrated to reach the ID through the microtubule highway [103][209][210][214]. Although the exact mechanism by which $Na_v1.5$ is targeted to the ID is not yet fully discovered, part of it is already elucidated. A few years ago, Agullo-Pascual et al. proved for the first time that the microtubule plus-end tracking protein “end-binding 1” (EB1) is captured to the IDs by connexin 43 (cx43), which

facilitates the cargo delivery, including $Na_v1.5$ [215]. These findings are consistent with Marchal and co-workers' recent study in which they have further proved that EB1 modulates $Na_v1.5$ trafficking to the IDs and that loss of EB1 function leads to reduced I_{Na} and conduction slowing [216]. Moreover, EB1 has been previously demonstrated to bind directly to CLASP2 (cytoplasmic linker associated protein 2) and form a complex at the microtubule plus-end, promoting thus microtubule polymerization and stabilization [217]. Interestingly, inhibiting the GSK3β (glycogen synthase kinase 3β)-mediated phosphorylation of CLASP2 enhanced the EB1–CLASP2 interaction, which in turn led to an increased $Na_v1.5$ delivery at the ID of cardiomyocytes and an increased I_{Na} [216]. Furthermore, Rhett et al. have shown that in addition to its known localization at the gap junction where it interacts with zonula occludens-1 (ZO-1) [218][219], Cx43 also co-localizes with ZO-1 in the zone surrounding the gap junction, conventionally termed as perinexus and that Cx43 but not ZO-1 interact with $Na_v1.5$ at this zone in physiological conditions [220]. In vivo and in vitro assays show that $Na_v1.5$ expression and function are reduced as a result of Cx43 expression/function decrease, thus giving more evidence that Cx43 is required for a proper $Na_v1.5$ function at the ID [221].

Importantly, $Na_v1.5$ and Cx43 interaction at the perinexus is thought to be mediated by scaffolding proteins SAP97 and Ankyrin G (AnkG) as their interaction has been reported [212][222]. In the cardiovascular system, ankyrins are critical components of ion channels and transporter signaling complexes, and their dysfunction has been linked with abnormal ion channel and transporter membrane organization and fatal human arrhythmias [223]. Although both ankyrin-B (AnkB, encoded by *ANK2*) and ankyrin-G (*ANK3*) have been found to be expressed in the myocardium, only ankyrin-G has been shown to interact with $Na_v1.5$ [224]. Specifically, AnkG is necessary for normal expression of $Na_v1.5$ and acts as a coordinating signaling center, functionally coupling $Na_v1.5$ gating with upstream kinase and phosphatase enzymes and downstream cytoskeletal proteins [80][225]. AnkG is primarily expressed at the ID membrane and T tubules, where it co-localizes with $Na_v1.5$ [112]. In vitro, it has been demonstrated that AnkG binds to $Na_v1.5$ and that AnkG downregulation impaired the subcellular localization of $Na_v1.5$ and reduced the I_{Na} current amplitude [226][227]. In vivo, Makara and his collaborators have demonstrated that AnkG plays an indispensable role in directing $Na_v1.5$ and its regulatory protein CaMKII to the ID [225][228]. Mutational studies have further confirmed that disrupting the binding of AnkG to $Na_v1.5$ impairs AnkG dependent targeting of the Na^+ channel to the ID leading thus to a reduction in I_{Na} density and cardiac arrhythmias [224][225][229]. A recent study performed by Yang et al. has demonstrated that AnkG, but not AnkB, are expressed at the IDs and that masking $Na_v1.5$ binding sites in AnkG using competitive peptides caused a decrease in sodium channel current (I_{Na}) and targeting defects of the Na^+ channels to the ID, but not to LM [184]. However, a more recent study by Cavus and collaborators specified that only canonical AnkG isoforms have this regulatory effect on $Na_v1.5$ and that noncanonical (giant) AnkG isoforms mediated electrical dysfunction is independent of $Na_v1.5$ [230].

Furthermore, AnkG is thought to mediate the interaction between Cx43 and PKP2, thus connecting desmosomal proteins with the molecular complex that captures the microtubule plus-end at the ID, thus allowing for delivery of $Na_v1.5$ [215][227][231]. This is consistent with the fact that loss of desmosomal integrity impacts cardiac conduction and leads to cardiac arrhythmias [231][232][233]. Accordingly, loss of Plakophilin-2 (PKP2), a crucial component of the cardiac desmosome, has been demonstrated to decrease I_{Na} in cardiac myocytes [234]. Similarly, loss of PKP2 expression in HL1 cells and in induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) from a patient with PKP2 deficiency reduced I_{Na} amplitude [232][235]. Likewise, Rizzo et al. have demonstrated that desmoglein-2

(Dsg2), another desmosome protein, physically interacts with $Na_v1.5$ at the ID of mouse cardiomyocytes in vivo [236]. They showed that mice models over-expressing a desmoglein-2 mutation present a wider intercellular space at the level of the ID, longer ventricular activation time, lower conduction velocity, lower upstroke velocity, and lower I_{Na} amplitude compared to wild type. Although no evidence of direct interaction between Desmoplakin (DSP) and $Na_v1.5$ has been reported, RNAi-based Desmoplakin silencing in vitro resulted in a reduction in $Na_v1.5$ expression at the ID of cardiomyocytes, an abnormal sub-cellular distribution of Cx43 and $Na_v1.5$, I_{Na} decay, and slowed conduction velocity suggesting that DSP regulates $Na_v1.5$ [237].

Similarly, AnkG is established as an adaptor protein that organizes, transports, and anchors $Na_v1.5$ to the actin/spectrin cytoskeleton [238][239][240]. In fact, the AnkyrinG-$Na_v1.5$ complex is believed to connect with the actin/α-spectrin cytoskeleton through CaMKII-β_{IV}-spectrin interaction where the latter acts as a CaMKII-anchoring protein and thereby orchestrating the whole macromolecular complex; however, no evidence of direct interaction between $Na_v1.5$ and β_{IV}-spectrin has been found yet [226]. On the other hand, β_{IV}-spectrin is assumed to control the CaMKII-dependent regulation of $Na_v1.5$ at the ID, and loss of β_{IV}-spectrin/CaMKII interaction precludes CaMKII-dependent phosphorylation of $Na_v1.5$ at Serine 571 in the DI–DII linker and abolishes the stress-induced activation of the pathogenic $I_{Na,L}$ [241][242].

Remme's team [243] has recently demonstrated that ID $Na_v1.5$ physically interacts with coxsackie and adenovirus receptor (CAR), a single-pass transmembrane cell adhesion molecule (CAM) [244]. Furthermore, they have demonstrated that CAR haploinsufficiency decreased I_{Na} amplitude at the ID, which in turn reduced sodium channel availability at this cell membrane compartment. $Na_v1.5$–CAR interaction is only beginning to be understood, and thus, mechanisms underlying this interaction are still to be studied.

Over the last decades, several controversial studies emerged regarding the sodium channel α-α-subunits interaction and dimerization. However, Clatot and co-workers settled this controversy by demonstrating for the first time that trafficking-defective $Na_v1.5$ exerts a dominant-negative effect on non-defective ones through α-α-subunits physical interaction at their N-terminal regions, precluding thus their cell surface expression [245]. Building on these findings, the team further evidenced that cardiac sodium channel α-subunits assemble as dimers with coupled gating and that this dimerization is mediated through an interaction site found within the DI-II linker of $Na_v1.5$, between amino acids 493 and 517 [246]. Curiously, earlier studies have shown that 14-3-3 protein, a member of highly conserved cytosolic acidic proteins, physically interacts with the DI-II linker of $Na_v1.5$ (between amino acid 417 and 467) at the ID and that this interaction facilitates the dimerization of cardiac sodium channels [247]. Strikingly, Clatot et al. identified a second 14-3-3 protein-$Na_v1.5$ interaction site between amino acid 517–555 and demonstrated that co-operative gating behavior but not dimerization of α-subunits is dependent on 14-3-3-$Na_v1.5$ interaction [246].

$Na_v1.5$ and the Lateral Membrane's Interactome

Dystrophin is known to indirectly mediate $Na_v1.5$ expression at the LM through binding to Syntrophin adapter protein which physically associates to the PDZ domain-binding motif at the C-terminal region of $Na_v1.5$ [3][212][248][249][250]. Interestingly, Matamoros et al. demonstrated that α1-syntrophin also interacts with the N-terminal region of $Na_v1.5$ through an "internal" PDZ-like binding domain localized at this region which acts as "chaperone-like"

domain that increases $Na_v1.5$ density at the LM and I_{Na} [251]. The same mechanism has been validated for Kir2.1 and Kir2.2 that were demonstrated to reciprocally interact with $Na_v1.5$ channels and modulate each other's trafficking and expression [251][252].

Interestingly, $Na_v1.5$ has been demonstrated to interact with CASK (calcium/calmodulin-dependent serine kinase), a member of the MAGUK protein family [253]. In several ways, CASK is considered an unconventional $Na_v1.5$ regulator since it is the only MAGUK protein that is lateral membrane-specific and also the only $Na_v1.5$ interacting protein that exerts a repressive effect on the functional expression of $Na_v1.5$, most likely by preventing its early trafficking to the LM. In this regard, CASK has been demonstrated to decrease I_{Na} when the former is over-expressed and to increase I_{Na} when CASK is inhibited in vivo and in vitro [253].

In addition, $Na_v1.5$ has been evidenced to interact with members of the Z-line scaffolding protein complex, such as α-actinin-2 and telethonin. While α-actinin-2 is currently known to physically interact with $Na_v1.5$ through the channel DIII–DIV linker [254], the telethonin interaction site on $Na_v1.5$ has not yet been identified [71]. α-actinin-2 is thought to positively regulate $Na_v1.5$ by increasing its cell surface expression, most likely through promoting its anchoring to the contact zones between T-tubules and Z-lines and connecting the channel to the actin cytoskeleton network [254]. However, scarce information is available regarding the mechanism of $Na_v1.5$ regulation by telethonin, although physical interaction between TCAP and $Na_v1.5$ was evidenced by co-immunoprecipitation methods and mutations in the telethonin coding gene (*TCAP*) has been found to alter the channel-gating properties of $Na_v1.5$ in patients with abnormal gut motility and Brugada syndrome [255][256].

Moreover, the role of fibroblast growth factor homologous factors (FHFs), a subset of the fibroblast growth factor (FGF) family [257], has been well elucidated modulating the neuron voltage-gated sodium channels [258]. However, their role in controlling cardiac sodium channel function is still poorly understood and subject to debate. In this respect, fibroblast growth factor homologous factor 1B (FHF1B), also known as FGF12B, has been reported to regulate the biophysical properties and kinetics of $Na_v1.5$ through its physical interaction (amino acids 1773–1832) with the $Na_v1.5$ C terminal region [259]. Both in vitro data show that FHF1B interacts with $Na_v1.5$, and this interaction results in hyperpolarizing shift in steady-state inactivation of this channel [259]. However, the opposite effect has also been reported where a depolarizing shift in the V1/2 of steady-state inactivation has been attributed to the FHF1B-$Na_v1.5$ interaction [260]. Furthermore, FGF13 (FHF2), which is the major FHFs in adult mouse hearts, has been identified as a $Na_v1.5$ interacting protein [260]. In the cardiomyocyte, FHF2 co-localizes with distinct $Na_v1.5$ pools, i.e., the LM and ID suggesting an important role for FHF2 modulating $Na_v1.5$ cell surface expression and function [261]. Like FGF12B, FGF13 physically binds to $Na_v1.5$ through the channel's C terminus region. In vivo, FGF13 knockdown altered $Na_v1.5$ function resulting in a decreased I_{Na} current density, reduced $Na_v1.5$ channel availability, slowed $Na_v1.5$, and reduced I_{Na} current recovery from inactivation [260]. This effect of FGF13 is isoform-specific [262]. FHFs have also been implicated in voltage-gated sodium channel trafficking control. In this context, FGF14 has been reported as a modulator of $Na_v1.5$ current densities in neurons and in the heart by impairing their biophysical properties or by controlling channel trafficking and cell surface expression in vitro [263].

Furthermore, calmodulin (CaM), a ubiquitous $Ca2^+$-sensing protein, has been reported to interact with $Na_v1.5$ N- and C-terminal regions [264][265][266][267] and the DIII–IV linker [144][265]. This interaction has been demonstrated to enhance slow inactivation and modulate $Na_v1.5$ gating [266], while disruption of CaM binding to $Na_v1.5$ decreases channel activity and enhances the propensity for persistent Na^+ current, all resulting from a switch in the Na_V inactivation mechanism [267]. $Na_v1.5$–CaM interaction has been further studied in a mutational context related to cardiac sodium channelopathies (See Section 4).

Finally, dipeptidyl peptidase-like protein-10 (DPP10), previously reported as a modulator of $K_v4.3$-current kinetics [268], has recently emerged as a new regulator of $Na_v1.5$ [269]. In vivo, DPP10 has been reported to modulate $Na_v1.5$ current kinetics as well by altering voltage dependence of Na^+ current and upstroke velocity of the action potential [269].

The Caveolar $Na_v1.5$

Cardiac sodium channels have also been localized to cardiomyocyte caveolae, which are specialized subsarcolemmal membrane compartments enriched in lipids and play a crucial role in vesicular trafficking and protein targeting to the cell surface [270][271]. Caveolar $Na_v1.5$ is exposed to a very rich macromolecular complex encompassing fatty acids, ion channels (pacemaker channels, potassium channels, calcium channels, etc.), and signaling complexes (G-protein-coupled receptors, protein kinases, etc.). This microenvironment has been reported to regulate $Na_v1.5$ function and membrane expression in a multilayers fashion [271].

The first layer is related to the biochemical properties of caveolae itself as a specialized lipid raft rich in fatty acids. In this regard, previous reports demonstrated that $Na_v1.5$ is blocked by polyunsaturated fatty acids (PUFAs), suggesting that interaction of $Na_v1.5$ with the caveolar lipids that also include PUFAs might have the same effect [272][273]. Nonetheless, the mechanism by which caveolar lipid rafts regulate $Na_v1.5$ is not yet fully understood.

The second layer of caveolar $Na_v1.5$ regulation is mediated by caveolins which are the major proteins of caveolae [271]. This mechanism was first reported by the Shibata group, which demonstrated that in addition to the indirect β-adrenergic regulation of $Na_v1.5$, which is PKA-dependent, stimulation of the β-adrenergic pathway in the presence of a PKA inhibitor, activates G-protein (Gsα) cascade, which in turn leads to a rapid increase of I_{Na} [270]. A subsequent study by the same group suggested that caveolar $Na_v1.5$ channels are stored at caveolae invaginations and that PKA-independent Gsα-dependant stimulation of the β-adrenergic pathway leads to the opening of caveolae, the exposition of $Na_v1.5$ channels to the extracellular environment, which in turn increase I_{Na} [274]. This mechanism has been completely neutralized by anti-caveolin 3 antibodies dialyzed into the myocytes suggesting that caveolar $Na_v1.5$ function is dependent on the Gsα-Caveolin 3 (Cav3) interaction [274]. Although $Na_v1.5$ has been confirmed to interact with caveolin 3 in rodent and human cardiomyocytes [270][275], it is not yet clear if this interaction is direct or indirect. Several reports suggested that Cav3 modulates $Na_v1.5$ function indirectly through inhibiting the nNOS, which is a part of the $Na_v1.5$-SNTA1-PMCA4b macromolecular complex [275][276].

3.1.6. Regulation of $Na_v1.5$ Degradation

Maintaining the balance between protein synthesis and degradation is crucial for the fine-tune regulation of $Na_v1.5$ levels [277]. In fact, it is currently well established that internalization and degradation of $Na_v1.5$ are regulated either by ubiquitination, covalent attachment of ubiquitin moieties [278], or autophagy [279]. The first mechanism is mediated by the interaction of C-terminus PY motifs of $Na_v1.5$ with the fourth tryptophan-rich domain (WW) of E3 ubiquitin ligase NEDD4-2, which leads to the labeling of $Na_v1.5$ by ubiquitin residues that will be later recognized by the degradation machine [70][280][281]. Interestingly, yeast two-hybrid data demonstrated that the interaction between $Na_v1.5$/αβ-Cristallin from one hand and αβ-Cristallin/Nedd4-2 from another hand reduced internalization of cell surface $Na_v1.5$ and ubiquitination of $Na_v1.5$ [282]. Similarly, serum and glucocorticoid inducible kinase (SGK) has been reported to regulate $Na_v1.5$ degradation by phosphorylating and inhibiting Nedd4-2 [283], whereas UBC9, a SUMO-conjugating enzyme, has been shown to promote $Na_v1.5$ ubiquitination [284]. A very recent study by Liu et al. demonstrated that $Na_v1.5$ ubiquitination would be downregulated by the association of FAT10, a small ubiquitin-like modifier, to the C-terminal lysine residues of $Na_v1.5$, thus decreasing the binding of $Na_v1.5$ to the Nedd4-2 and preventing its degradation [285].

Nedd4-2 has been reported as a direct target of AMP-activated protein kinase (AMPK) in epithelial cells [286]. However, a recent report by Liu X et al. attributed a Nedd4-2 independent $Na_v1.5$ degradation mechanism to AMPK [279]. AMPK, through phosphorylating $Na_v1.5$ T101 residue, facilitates the association of the channel to the autophagic adapter protein and microtubule-associated protein 1 light chain 3 (LC3) and exposes the complex to the autophagic degradation machinery [279].

3.1.7. Effect of Gonadal Hormones on $Na_v1.5$ Expression and Function

The male predominance of some sodium channelopathies such as Brugada syndrome has been extensively studied over the last few years, thus questioning a possible link between sex hormones and $Na_v1.5$ [287][288]. However, comparing the expression levels of $Na_v1.5$ between normal male and female human hearts showed no difference [289]. In addition, concentration-related block of $Na_v1.5$ by estradiol showed that estradiol could not reduce the current of $Na_v1.5$ [290], although a slight reduction in I_{Na} currents has been observed at a high concentration of estradiol in vitro [291]. Yang et al. have recently studied the expression levels and function of $Na_v1.5$ in HEK293 cells co-expressing *SCN5A* (wild-type or BrS mutants R878C and R104W) and sex hormone receptors. They whereby showed that sex hormones have no effects on the expression level of *SCN5A* (either WT or mutant) and I_{Na} currents [292]. Similarly, gonadal hormones testosterone and estrogen showed no effect on fast I_{Na} in a canine model [293]. However, a recent study by Hu et al. demonstrated that estrogen through its rapid signal receptor GPER ameliorated the damaging effects of stress in human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) model mimicking β-adrenergic overstimulation [294].

3.1.8. Effect of Temperature and pH on $Na_v1.5$ Expression and Function

Febrile states and acidosis are two environmental factors that have been extensively studied as non-genomic modulators of $Na_v1.5$ function in health and disease. It is currently well known that $Na_v1.5$ kinetic is temperature and pH-sensitive [295]. In this context, mild hypothermia has been described as an antiarrhythmic factor that maintains myocardial conduction during prolonged ischemia by sustaining $Na_v1.5$ and Cx43 function [296], whereas

hyperthermia has been described as a proarrhythmic factor, especially in combination with *SCN5A* mutations as is the case in Brugada syndrome [297][298][299][300]. Two mechanisms have been suggested so far for the temperature-dependent regulation of $Na_V1.5$. The first one is a direct mechanism by which temperature accelerates the inactivation of only the wild-type $Na_V1.5$ channels in heterozygous patients, which results in the misbalance between depolarization and repolarization currents and thus may lead to fever-induced arrhythmias [26][301]. The second mechanism is indirect by which temperature modulates the function of $Na_V1.5$ interacting proteins, which in turn modulate $Na_V1.5$ function as is the case of FGF13 [302].

Similarly, fluctuation of the extracellular pH has been demonstrated to influence the $Na_V1.5$ function. For instance, acidic extracellular pH has been shown to modify wild-type $Na_V1.5$ kinetics by destabilizing both the fast inactivated and the slow inactivated states of $Na_V1.5$ [303]. In addition, it has been reported that extracellular protons disrupt charge immobilization which leads to the destabilization of the $Na_V1.5$ fast-inactivation through direct interaction with outer ring carboxylates of the $Na_V1.5$ DIII or DIV [304]. Particularly, His-880 and Cys-373 were identified as the key mediator of $Na_V1.5$ sensitivity to pH fluctuation, where Cys-373 is responsible for isoform-specific proton modulation of use-dependent inactivation of $Na_V1.5$ [305].

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