Life Cycle of the Cardiac Voltage-Gated Sodium Channel Na\textsubscript{V}1.5

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Cardiac voltage-gated sodium channel Na\textsubscript{V}1.5, encoded by SCN5A, is crucial for the upstroke of action potential and excitation of cardiomyocytes. Na\textsubscript{V}1.5 undergoes complex processes before it reaches the target membrane microdomains and performs normal functions. A variety of protein partners are needed to achieve the balance between SCN5A transcription and mRNA decay, endoplasmic reticulum retention and export, Golgi apparatus retention and export, selective anchoring and degradation, activation, and inactivation of sodium currents. Subtle alterations can impair Na\textsubscript{V}1.5 in terms of expression or function, eventually leading to Na\textsubscript{V}1.5-associated diseases such as lethal arrhythmias and cardiomyopathy.

Keywords: Na\textsubscript{V}1.5, SCN5A, biosynthesis, trafficking, anchoring, degradation, gating modulation, post-transcriptional modification

INTRODUCTION

The cardiac voltage-gated sodium channel Na\textsubscript{V}1.5 is made up of a 220-kDa pore-forming \(\alpha\)-subunit and 30-kDa auxiliary \(\beta\)-subunits. For the convenience of reading, Na\textsubscript{V}1.5 in the following parts refers to the \(\alpha\)-subunit of Na\textsubscript{V}1.5. The SCN5A gene, found on chromosome 3p21, encodes the Na\textsubscript{V}1.5 channel, which includes four homologous domains (DI-DIV), a C-terminus, and an N-terminus (Figure 1). Each domain of the Na\textsubscript{V}1.5 channel is composed of six membrane-spanning segments (S1-S6). Specifically, the S4 transmembrane segment acts as a voltage sensor. The S5 and S6 transmembrane segments form a pore with the intermembrane P-loop, which determines ion selectivity and influx (Jiang et al., 2020). The Na\textsubscript{V}1.5 channel mediates the rapid influx of sodium ions (Na\textsuperscript{+}), which triggers cardiac action potential (AP), induces rapid depolarization, and initiates the excitation-contraction coupling cascades in the cardiomyocytes (Han et al., 2018). The sodium current (\(I_{Na}\)) generated by Na\textsubscript{V}1.5 is determined by the channel density on the plasma membrane and channel gating. Na\textsubscript{V}1.5 is traditionally regarded as a monomer. However, it is well accepted that Na\textsubscript{V}1.5 is assembled as a dimer and exhibits coupled gating properties (Clatot et al., 2017). \(\beta1-\beta4\) subunits, encoded by the SCN1b-4b genes, consist of an extracellular N-terminus, a transmembrane \(\alpha\)-helix, and an intracellular C terminus (Salvage et al., 2020). The \(\beta\)-subunits act as gating modulators of Na\textsubscript{V}1.5 and facilitate Na\textsubscript{V}1.5 residence at the intercalated disk.

The life cycle of Na\textsubscript{V}1.5 begins with the transcription of the SCN5A gene and RNA processing. Then, Na\textsubscript{V}1.5 proteins are synthesized at the rough endoplasmic reticulum (ER) and follow the secretory pathway to reach the plasma membrane where the proteins exert their respective function. Various proteins are reported to be involved in the biosynthesis, trafficking, anchoring,
post-transcriptional modification, gating regulation, and degradation of NaV1.5 by directly or indirectly interacting with the different motifs and domains of NaV1.5.

The aim of this review is to provide an updated account of the life cycle of NaV1.5, while summarizing SCN5A-related diseases and novel therapeutic strategies targeting NaV1.5.

**BIOSYNTHESIS**

Gene expression in eukaryotes starts with transcription, the transition of a DNA sequence into an RNA transcript (known as precursor mRNA) assisted with RNA polymerase and transcription factors. The precursor mRNA is the copying of the coding and noncoding genes which then need to undergo splicing and post-transcriptional modifications to produce mature mRNA and ultimately translate into polypeptides (Figure 2). The human SCN5A gene spans approximately 8,000 bp and consists of 28 exons, which can be spliced together to generate the full-length NaV1.5 protein (about 2016 amino acids). Exons 2–28 encode the protein-coding sequence. Exon 1 and part of exon 2 encode the mRNA 5′-untranslated region (5′-UTR). Exon 28 encodes the mRNA 3′-UTR (Wang et al., 1996). The transcription of the SCN5A gene is regulated by various transcription factors. Positive transcription factors such as TBX5 and NF-κB increase SCN5A mRNA abundance and further increase the expression and current of NaV1.5, while negative transcription factors such as FOXO1 and Snail show the opposite effects (Table 1). MicroRNAs (miRNAs) regulate gene expression through translational repression or mRNA degradation. miR-192-5p is reported to negatively regulate the expression of NaV1.5 and reduce $I_{Na}$ density by interacting with the 3′-UTR of human SCN5A mRNA (Zhao et al., 2015).

Alternative splicing creates multiple variants of NaV1.5 including functional and nonfunctional types (Schroeter et al., 2010). Compared to full-length NaV1.5, spliced NaV1.5 variants like NaV1.5a, NaV1.5d, and NaV1.5e present altered electrophysiological kinetic properties; NaV1.5c show unchanged electrophysiological properties; NaV1.5b, NaV1.5f, and truncated variants E28B-E28D do not generate currents (Schroeter et al., 2010). The splicing machinery might explain the inconsistent genotype-phenotype outcomes. For instance, the LQT3-associated mutation SCN5A-T1620K showed electrophysiological properties similar to those of hNaV1.5, hNaV1.5a, and hNaV1.5c, but different effects in the hNaV1.5d background (Gaetano et al., 2011). Nevertheless, the exact mechanisms of NaV1.5 splicing regulation are still unclear but involve species-dependent, tissue-specific, and developmental factors.

NaV1.5 splice variants are reported to be involved in the pathophysiology of heart failure (HF), SCN5A channelopathies, and myotonic dystrophy. With angiotensin II (AngII) or hypoxia stimuli (signals common to HF), activated splice factors RBM25 and hLuc7A increase NaV1.5 splice variants E28C and E28D. Increased E28C and E28D variants cause a reading frame shift and encode truncated Na$^+$ channels before DIV of the channel due to premature stop codons (Gao et al., 2011). The nonfunctional channels are trapped in the endoplasmic reticulum (ER) and trigger the unfolded protein response (UPR). UPR activation further leads to destabilization of the remaining full-length SCN5A mRNA, exacerbating the reduction of $I_{Na}$ (Gao et al., 2013; Noyes et al., 2017). Studies also found that SCN5A splicing in cardiomyocytes and white blood cell (WBC) changes in a correlated manner during HF. If altered WBCs SCN5A variants were proven to increase the risk of sudden death or other HF-associated arrhythmias, a blood examination...
FIGURE 2 | Biosynthesis and trafficking of Na\textsubscript{V}1.5. TBX5, T-box transcription factor 5; NF-\textkappa-B, nuclear factor kappa-B; Irx3, Iroquois homeobox 3; MEF2C, myocyte enhancer factor-2C; Forkhead box O1; Nup107, nucleoporin 107; PKA, protein kinase A; Cx43, connexin 43; PKP-2, plakophilin 2; MAGUK, membrane-associated guanylate kinase; DMC, dystrophin-syntrophin multiprotein complex; CASK, calcium/calmodulin-dependent serine protein kinase; FGF, fibroblast growth factor; CaMKII, Ca\textsuperscript{2+}/calmodulin-dependent kinase II.

TABLE 1 | Transcription factors of Na\textsubscript{V}1.5 and their binding sites.

| Transcription Factors | Binding Sites | Effects | References |
|-----------------------|---------------|---------|------------|
| Positive              |               |         |            |
| TBX5                  | an enhancer downstream of the SCN5A gene | The knockout of TBX5 from the mature murine ventricular conduction system markedly decreases the density of Na\textsubscript{V}1.5, increases arrhythmias propensity, and results in sudden cardiac death. | Arnolds et al., 2012; Ivan et al., 2004; Sternle and Moskowitz, 2017 |
| NF-\textkappa-B       | the SCN5A promoter region | Treatment with angiotensin II (AngII) or H\textsubscript{2}O\textsubscript{2} enhances the binding capacity of NF-\textkappa-B with NF-\textkappa-B binding sequence, thus significantly decreasing the SCN5A mRNA levels and \textit{I}_{Na} in the H9C2 myocytes. Mutations in the NF-\textkappa-B binding site at the SCN5A promoter region mitigates the decreased activity of Na\textsubscript{V}1.5 in response to AngII and H\textsubscript{2}O\textsubscript{2}. | Shang and Dudley, 2005; Shang et al., 2008 |
| GATA4/5               | within the SCN5A proximal promoter and intron 1 regions | GATA4 and GATA5 bind to the GATA binding site within the SCN5A proximal promoter and intron 1 regions to synergistically activate the SCN5A gene in the human left ventricle samples. The GATA4\textsuperscript{+/−} heterozygous mice exhibited short PR intervals. | Brewer and Pizzey, 2006; Munshi et al., 2009; Schluterman et al., 2003; Tarradas et al., 2017 |
| IRX3                  | within the SCN5A promoter region | In the HL-1 cardiomyocytes and neonatal mouse ventricular myocytes, overexpression of IRX3 upregulated the mRNA levels of SCN5A and Cx40, which was not observed by overexpressing mutant IRX3. Deletion of IRX3 and IRX5 in the myocardium prolonged the atrioventricular conduction, which is partly due to the activation of Na\textsubscript{V}1.5 expression. | Gaborit et al., 2012; Koizumi et al., 2016 |
| MEF2C                 | within the SCN5A promoter region | Hu antigen R (HuR) increased the mRNA expression of MEF2C by inhibiting MEF2C mRNA decay and consequently enhancing SCN5A mRNA transcription. Consistently, these effects were attenuated upon transfecting the cardiomyocytes with MEF2C siRNA. | Zhou et al., 2018a; Zhou et al., 2018b |
| Negative              |               |         |            |
| FOXO1                 | E-box sites in the SCN5A core promoter | FOXO1 negatively regulated Na\textsubscript{V}1.5 expression by binding to the SCN5A promoter and inhibiting its activity in the HL-1 cardiomyocytes. Deletion of FOXO1 increased the mRNA and protein levels of Na\textsubscript{V}1.5 and \textit{I}_{Na} in the ventricular myocytes. | Cai et al., 2014; Mao et al., 2012 |
| Snail                 |               | Overexpression of Snail in mice resulted in downregulated SCN5A mRNA level, reduced Na\textsubscript{V}1.5 level and decreased \textit{I}_{Na}. CNS28\textsuperscript{−/−} mice, which disrupted the Snail-binding region regulator, exhibited significantly upregulated SCN5A mRNA level, increased Na\textsubscript{V}1.5 level and enhanced \textit{I}_{Na} in the freshly isolated ventricular myocytes. | Atack et al., 2011; Hesse et al., 2007; Nieto, 2002 |
to predict HF-associated arrhythmic risk would be possible (Gao and Dudley, 2013).

**TRAFFICKING AND ANCHORING**

SCN5A mRNA exported from the nucleus is translated to protein and assembled in the rough ER. Next, the protein is translocated to the Golgi apparatus for further modification. After exiting the Golgi apparatus, NaV1.5 settles in the plasma membrane to exert its functions.

**Nucleus Export**

Nuclear pore complexes, also known as nucleoporins, mediate the exchange of molecules between the nucleoplasm and cytoplasm. Nucleoporin 107 (Nup107) selectively facilitates the export of SCN5A mRNA from the nucleus to cytoplasm without affecting the SCN5A mRNA level (Guan et al., 2019). Additionally, increased Nup107 and NaV1.5 were observed in the cardiomyocytes and heart tissues under hypoxic and oxidative stress conditions. This suggests that Nup107 is a protein that reacts rapidly to the insults and can be developed as a novel molecular therapeutic target for myocardial ischemic damage.

As of writing, it is not clear whether there are other nucleoporins that take part in the nucleus-cytoplasmic trafficking of SCN5A mRNA. MOG1 is found to interact with Ran GTP, a small protein that mediates the nuclear import and export of proteins and RNA (Steggerda and Paschal, 2001). MOG1 is shown to promote intracellular trafficking of NaV1.5 from the ER (Yu et al., 2018). Thus, MOG1 may also play a regulatory role in the nucleus-cytoplasmic trafficking of SCN5A mRNA.

**ER Export**

ER is the first station of the secretory pathway where the processes of protein folding, quality control, and protein complex assembly take place. Several ER retention and export motifs have been identified in ion channels (Mikosch and Homann, 2009; Benyair et al., 2011). ER export motifs are crucial for efficient ER export of mature and properly folded proteins through coat protein II (COPII) vesicles. COPII-coated vesicles in association with Sec23/24, Sec13/31, Sar1, and Sec12 mediate anterograde protein trafficking between the ER and Golgi (Kurokawa and Nakano, 2019). MOG1 facilitates the export of NaV1.5 from the ER and improves NaV1.5 expression on the cell surface, probably by interacting with Sar1A and Sar1B (Chakrabarti et al., 2013; Wang et al., 2018; Yu et al., 2018; Kurokawa and Nakano, 2019). It is now recognized that ER retention signals can also play an important role in ER export of many plasma membrane proteins. After masking the ER retention signals, the proteins seem to receive an “exit card” and are released from the ER. The DI-II linker region of NaV1.5 contains three putative RXX-type ER retention motifs (479RRK481, 533RRR535, and 659RRQ661). Protein kinase A (PKA)-mediated phosphorylation of NaV1.5 masks the retention signals in the DI-II linker region of NaV1.5, and promotes the export of NaV1.5 from the ER to the Golgi (Zhou et al., 2002; Rook et al., 2012).

Nevertheless, the ER export mechanism of NaV1.5 is still poorly understood. Rab GTPases, the largest members of the Ras superfamily, play an important role in protein trafficking between intracellular compartments in eukaryotes (Li and Marlin, 2018). Rab1 and Rab2 are reported to regulate protein transport between the ER and Golgi, but their role in NaV1.5 trafficking is uncertain and needs to be tested in further studies.

**Golgi Export**

Selective Golgi export of proteins from the Golgi to the plasma membrane is another key step in protein trafficking, which has been studied in inward-rectifying potassium channels (Li et al., 2016). However, little is known about the regulation of NaV1.5 transport from the Golgi. It is speculated that Golgi retention and export motifs possibly modulate NaV1.5 exit from the Golgi (Gao et al., 2014).

**Anchoring**

Cardiac NaV1.5 channels are arranged in clusters, also called pools, in the following membrane microdomains of cardiomyocytes: intercalated discs (ID), T-tubules, costameres, and caveolae. ID mainly consist of three intercellular adhesion structures namely, gap junctions, adherens junctions, and desmosomes (Clark et al., 2002). ID is responsible for electromechanical coupling. The upstroke of AP caused by Na\(^{+}\) influx through NaV1.5 channels can spread quickly through IDs to ensure the coordinated excitation and contraction among cardiomyocytes. T-tubules are tubular invaginations of the lateral sarcolemma that link the sarcoplasmic reticulum and initiate excitation-contraction coupling. AP mediated by NaV1.5 is transmitted along the T-tubules, induces calcium release, and further triggers the contraction of cardiomyocytes. Costameres are sarcomembran transverse rib-like structures that adhere adjacent cardiomyocytes to the extracellular matrix and maintain the three-dimensional structure of the myocardium (Balse and Eichel, 2018). Caveolae are 50–100 nm cave-like invaginations of the plasma membrane that are made up of essential scaffolding proteins called caveolins. Besides sodium channels (NaV1.5), L-type calcium channels, potassium channels (K\(_{v}1.5\)), sodium-calcium exchanger, and Na\(^{+}/K^{+}\) ATPase have been subcellularly localized to caveolae and may allow these channels to be integrated into macromolecular complexes to exert their functions and to be regulated in a unified manner (Bali and Kamp, 2008). T-tubules, costameres, and caveolae are all located in the lateral membranes of cardiomyocytes. NaV1.5 channels are located in different membrane microdomains of cardiomyocytes, which are determined by their specific partners, such as cytoskeleton-binding proteins, gap junctional proteins, and desmosomal proteins (Table 2; Balse and Eichel, 2018).

To our knowledge, a sorting process at the early stages possibly exists, which affects the final anchoring of membrane proteins toward specific microdomains. To better understand the mechanism of NaV1.5 anchoring, it is of great value to investigate the complex processes of sorting, identification by protein chaperones, and organization of microdomains, both in physiological and pathological conditions.
stimulation was reported to downregulate Na$^{+}$ plays a major role in mediating the autophagic degradation of Adenosine 5′-monophosphate-activated protein kinase (AMPK) plays a major role in mediating the autophagic degradation of Na$\text{\textsubscript{v}}$1.5 during cardiac ischemia and reperfusion (I/R) injury. I/R stimulation was reported to downregulate Na$\text{\textsubscript{v}}$1.5 abundance in rat hearts. An *in vitro* study showed that under conditions of I/R stress, Na$\text{\textsubscript{v}}$1.5 was degraded through the AMPK-mediated autophagic pathway rather than through the proteasome pathway (Tang et al., 2019). AMPK assists Na$\text{\textsubscript{v}}$1.5 to bind to the autophagic adapter protein and microtubule-associated protein 1 light chain 3 (LC3) by phosphorylating Na$\text{\textsubscript{v}}$1.5 at threonine (T) 101, and enhances the subsequent degradation through the autophagic pathway (Liu et al., 2019).

**TABLE 2 |** Protein partners associated with Na$\text{\textsubscript{v}}$1.5 localization in the cardiomyocytes.

| Classification          | Representation   | Localization            | References                      |
|-------------------------|------------------|-------------------------|--------------------------------|
| Cytoskeleton-binding proteins | ankyrin-G        | intercalated disks      | Makara et al., 2014; Yang et al., 2020 |
| Gap junctional proteins  | Connexin 43      | intercalated disks      | Bruce et al., 2008; Sottas et al., 2018 |
| Desmosomal proteins     | Desmoglein 2     | intercalated disks      | Rizzo et al., 2012               |
| Desmosomal proteins     | Desmoplakin      | intercalated disks      | Zhang et al., 2013               |
| Dystrophin–syntropin complex | Dystrophin      | lateral membranes       | Gavillet et al., 2006            |
| Caveolins               | Caveolin-3       | Caveolae                | Cheng et al., 2013; Gavillet et al., 2006; Schilling et al., 2016; Vaidyanathan et al., 2018 |
| MAGUK proteins          | SAP97            | intercalated disks      | Petitprez et al., 2011           |
|                         | CASK             | lateral membranes       | Eichel et al., 2016              |

**DEGRADATION**

The last step of the Na$\text{\textsubscript{v}}$1.5 channel life cycle is degradation, which can be considered as a form of retrograde trafficking (Figure 3). There are two major pathways for the degradation of Na$\text{\textsubscript{v}}$1.5: the proteasome and autophagic degradation pathways.

**Proteasome Degradation Pathway**

Ubiquitination is a common signal for protein internalization and degradation. E3 ubiquitin ligase Nedd4-2 contains WW domains, an N-terminal calcium/protein binding C2 domain, and a C-terminal HECT domain. When the C2 domain binds to the HECT domain, Nedd4-2 presents an inactive state. When Ca$^{2+}$ binds to the C2 domain, the HECT domain is exposed and Nedd4-2 is activated. Activated Nedd4-2 binds to the PY motifs of target proteins through its WW domains for ubiquitination (Lamothe and Zhang, 2016). Ion channels tagged with ubiquitin are usually compartmentalized into vesicles destined for degradation (by the lysosomal or proteasomal system) or recycled back to the membrane via small GTPase Rabs. Nedd4-2 binds to the PY motif of Na$\text{\textsubscript{v}}$1.5 through post-transcriptional modifications (PTMs), such as glycosylation, phosphorylation, methylation, and ubiquitylation. PTMs, such as PKA- and CaMKII-mediated phosphorylation and Nedd4-2-mediated ubiquitylation have been discussed in the former sections. We will put more emphasis on the glycosylation, SUMOylation, methylation, and acetylation of Na$\text{\textsubscript{v}}$1.5 in the following sections.

**POST-TRANSCRIPTIONAL MODIFICATIONS**

Interacting proteins modify the structure and properties of Na$\text{\textsubscript{v}}$1.5 through post-transcriptional modifications (PTMs), such as glycosylation, phosphorylation, methylation, acetylation, and ubiquitylation. PTMs, such as PKA- and CaMKII-mediated phosphorylation and Nedd4-2-mediated ubiquitylation have been discussed in the former sections. We will put more emphasis on the glycosylation, SUMOylation, methylation, and acetylation of Na$\text{\textsubscript{v}}$1.5 in the following sections.

**MODULATION OF THE GATING PROPERTIES**

Na$\text{\textsubscript{v}}$1.5 activation depends on the S4 segment, which contains multiple positively charged amino acids that move across the membrane in response to changes in membrane potential. The voltage-sensing domain (VSD), formed by S1-S4, rotates when membrane depolarization moves the S4 segment within DI–DIII outward relative to other channel segments. This allows Na$^{+}$ to flow inwardly through the pores composed of the S5 and S6 segments and the P loop. Early I$\text{\textsubscript{Na}}$ induces rapid AP upstroke, leading to further channel activation. Na$\text{\textsubscript{v}}$1.5 inactivation involves two distinct processes: fast and slow inactivation. Fast inactivation is coupled to the activation process and occurs within milliseconds. This process may involve an isoleucine-phenylalanine methionine (IFM) motif, which is a highly conserved amino acid triplet in the III–IV linker (Chadda et al., 2017). Unlike fast inactivation, slow inactivation is not coupled to the activation process and can last for as long as a few seconds. Conformational modifications in the following three domains drive the slow inactivation process: the trans-membrane segment S4/D4, the loop between SS-S6/DII (P-loop/DII), and segment S6/DII (Detta et al., 2015). When Na$\text{\textsubscript{v}}$1.5 channels do not completely inactivate, a lasting current less than 0.5% of the peak current can be detected in the cardiomyocytes, which is known as late I$\text{\textsubscript{Na}}$ (I$\text{\textsubscript{Na–L}}$). Because of the short duration of the AP plateau, I$\text{\textsubscript{Na–L}}$ can result in situations where the Na$^{+}$ “load” becomes twice as much as peak I$\text{\textsubscript{Na}}$ over time, and this plays an important role in angina, arrhythmia, and HF (Makielski, 2016). Many proteins have been identified to modulate the gating properties of Na$\text{\textsubscript{v}}$1.5, such as β-subunits, FGF, CaMKII, and 14-3-3. Their interacting domains and modulation effects are summarized in Table 3.
FIGURE 3 | Internalization and degradation of Na\textsubscript{V}1.5 on the plasma membrane. Nedd4-2, neural precursor cell-expressed developmentally downregulated 4 type 2; SGK, serum- and glucocorticoid-inducible kinase.

Glycosylation

Many ion channels are known to contain glycan moieties oriented toward the outside of the membrane, which are anchored to residues, such as serine, threonine (O-linked glycosylation), or asparagine (N-linked glycosylation) (Marionneau and Abriel, 2015). Sialic acids, which are negatively charged terminal residues, are subsequently linked with N-glycans or O-glycans through trans-Golgi sialyltransferase activity and contribute to the extracellular surface potential. The Na\textsubscript{V} is a heavily N-glycosylated protein with carbohydrates that make up 20 to 30% of total mass. However, Na\textsubscript{V}1.5 is an exception, with approximately 5% by weight of carbohydrates (Mercier et al., 2015). N-glycosylation, which is initiated in the ER and terminated in the Golgi apparatus, is reported to be essential for membrane localization and gating properties. The D25N mutation of the \(\beta\)1 subunit resulted in decreased targeting of Na\textsubscript{V}1.5 to the plasma membrane due to a maturation (glycosylation) defect (Baroni et al., 2018). Ventricular Na\textsubscript{V} from ST3Gal4 (a glycogene responsible for glycoprotein sialylation) deficient mice is reported to exhibit gating at higher depolarized potentials, slower inactivation, and faster recovery than in control mice (Ednie et al., 2013).

Methylation

Arginine methylation within the interdomain linker between DI and DII of Na\textsubscript{V}1.5 is catalyzed by protein arginine methyltransferases (PRMT), which transfer methyl groups from the cofactor S-adenosyl-L-methionine (SAM) to the protein. Arginine methylation is an important PTM in voltage-gated ion channels. PRMT-3 and -5 methylate Na\textsubscript{V}1.5 and increase Na\textsubscript{V}1.5 current density by increasing the cell surface expression in HEK293 cells (Beltran-Alvarez et al., 2013). Arginine methylation of Na\textsubscript{V}1.5 is also detected in the human heart tissue of patients with end-stage HF. Additionally, R526 methylation is identified as the major Na\textsubscript{V}1.5 methylation site in patients with end-stage HF (Beltran-Alvarez et al., 2014). Moreover, the methylation-phosphorylation crosstalk of Na\textsubscript{V}1.5 has been previously reported. Na\textsubscript{V}1.5 methylation at R513 significantly decreased S516 phosphorylation, which consequently hindered R513 methylation (Beltran-Alvarez et al., 2015).

Acetylation

N-terminal acetylation, which is irreversibly catalyzed by ribosome-associated N-terminal acetyltransferases (NATs), is a major PTM of eukaryotic proteins that regulates protein–protein interactions and membrane targeting. Recently, N-terminal acetylation has been reported to be a degradation signal that inhibits protein targeting to the secretory pathway (Arnesen, 2011). N-terminal acetylation of Na\textsubscript{V}1.5 at the initial 30 alanine residues was discovered in the hearts of patients with end-stage HF (Beltran-Alvarez et al., 2014). In contrast, N-lysine acetylation, which is catalyzed by histone acetyltransferases (HATs), can be reversed by histone deacetylases and sirtuins. Sirtuin1 deacetylase-mediated acetylation at lysine 1479 of
TABLE 3 | Proteins and their modulation effects on the gating properties of Na\textsubscript{v}1.5 channels.

| Proteins | Interacting domains | Modulation effects of gating properties | References |
|----------|---------------------|----------------------------------------|------------|
| \(\beta\)-subunits | \(\beta1\) | DIV-VSD | Co-expression of \(\beta1\) with cardiac Na\textsubscript{v}1.5 increased \(I_{Na}\) amplitude, resulting in a depolarizing shift in steady-state inactivation and enhances recovery from inactivation. Overexpressing \(\beta1\) caused significant hyperpolarizing shifts in both activation and inactivation kinetics, and greatly reduced persistent \(I_{Na-L}\) in the Chinese hamster ovary cells stably expressing human Na\textsubscript{v}1.5. | Fahmi et al., 2001; Ko et al., 2005; Zhu et al., 2017 |
| | \(\beta2\) | | Co-expression of \(\beta2\) with Na\textsubscript{v}1.5 caused a negative shift in activation in Pro5 and LeC2 cells. Co-expression of \(\beta2\) with Na\textsubscript{v}1.5 caused a positive shift in inactivation in Chinese hamster ovary cells. | Johnson and Bennett, 2006; Watanabe et al., 2009 |
| | \(\beta3\) | DIII-VSD | Overexpressing \(\beta3\) accelerated macroscopic current decay, caused hyperpolarizing shifts in both activation and inactivation kinetics, slowed recovery from inactivation, and greatly reduced persistent \(I_{Na-L}\) in the Chinese hamster ovary cells stably expressing human Na\textsubscript{v}1.5. | Ko et al., 2005; Zhu et al., 2017 |
| | \(\beta4\) | | Controversial. Medeiros-Domingo’s study showed that overexpression of \(\beta4\) with Na\textsubscript{v}1.5 significantly increased the slope factors of both activation and inactivation, shifted the inactivation curve to a more negative potential, and reduced slow recovery from inactivation in HEK293 cells stably expressing Na\textsubscript{v}1.5. Tan’s study showed that co-expression of \(\beta4\) with Na\textsubscript{v}1.5 did not affect the activation or recovery from inactivation of the cardiac sodium current, but significantly shifted the activation curve to a more negative potential in HEK293 cells. However, in Qin Yang’s study, they did not observe any significant effect. | Medeiros-Domingo et al., 2007; Tan et al., 2010; Yang et al., 2019 |
| FGF | FGF12 C-terminus | Overexpression of FGF12 exhibited a significant hyperpolarizing shift in voltage-dependent inactivation without affecting the activation of Na\textsubscript{v}1.5. | Liu et al., 2003 |
| | FGF13 C-terminus | The knockout of FGF13 in adult mouse ventricular myocytes delayed recovery from inactivation of Na\textsubscript{v}1.5. | Wang et al., 2011 |
| CaMKII | IQ motif | Overexpressing CaMKII exhibited a depolarizing shift in sodium channel inactivation and increased \(I_{Na-L}\) in rabbit, mouse and the guinea pig ventricular cardiomyocytes. Its effects on recovery from inactivation and intermediate or slow inactivation of Na\textsubscript{v}1.5 are controversial. | Aiba et al., 2010; Wagner et al., 2006 |
| 14-3-3\(\eta\) | the first interdomain of Na\textsubscript{v}1.5 between amino acids 417 and 467 | The co-expression of Na\textsubscript{v}1.5, \(\beta1\) subunit and 14-3-3\(\eta\) in the COS-7 cells resulted in a negative shift in inactivation and a delayed recovery from inactivation without changes in the activation and current density. 14-3-3\(\eta\) mediated coupled gating. | Alousi et al., 2006; Clatot et al., 2017 |

Na\textsubscript{v}1.5 results in enhanced trafficking to the surface of the plasma membrane and increased \(I_{Na}\) (Yoon et al., 2017).

**SUMOylation**

SUMOylation, a PTM, is analogous to ubiquitylation involving an enzymatic cascade. In contrast to ubiquitylation, SUMOylation involves conjugating the proteins to small ubiquitin-like modifiers (SUMOs). SUMOylation can affect protein structure and subcellular localization. Recently, Na\textsubscript{v}1.5 was reported to be SUMOylated only at lysine 442. The mutation of lysine 442 or application of a deSUMOylating enzyme inhibits hypoxic reopening in response to hypoxia. SUMOylation of Na\textsubscript{v}1.5 is associated with an increase in \(I_{Na-L}\) (Plant et al., 2020).

Recently, novel post-transcriptional modifications have been reported. Zhang et al. found that an endogenous “lactate clock” turns on gene expression to promote homeostasis in bacterially challenged M1 macrophages (Zhang et al., 2019). The presence of histone lactylation represents a new avenue for understanding the pathophysiological mechanism of many diseases, including ischemic cardiovascular disease. It has been established that Na\textsubscript{v}1.5 channels are significantly downregulated under conditions of ischemia and hypoxia, which is accompanied by the accumulation of lactic acid. Whether lactylation is involved in the regulation of Na\textsubscript{v}1.5 under pathological conditions has not yet been revealed.

**SCN5A-RELATED DISEASES AND POTENTIAL THERAPY STRATEGY**

Na\textsubscript{v}1.5 is associated with the pathogenesis of various cardiovascular diseases, such as arrhythmia, ischemic cardiomyopathy, heart failure, and sudden cardiac death. Most cases of cardiac arrhythmia and sudden cardiac death are caused by SCN5A-related mutations, which change Na\textsubscript{v}1.5 expression and function. The gain-of-function mutations in SCN5A, which lead to increased \(I_{Na-L}\), can lead to long QT syndrome 3 (LQT3). Loss-of-function mutations in SCN5A, which lead to decreased \(I_{Na}\), can cause Brugada syndrome (BrS), sick sinus node syndrome, and atrial fibrillation (Li et al., 2018). To date, the reported BrS-associated SCN5A mutations and LQT3-associating mutations are over 300 and over 80,
respectively. Previous studies have demonstrated that Na\textsubscript{V}1.5 expression is downregulated in HF (Luo et al., 2017). The upregulated expression of Nedd4-2, co-localization of Nedd4-2 with Na\textsubscript{V}1.5, and increased diastolic calcium concentrations were observed in the volume-overloaded HF rat model, suggesting that Nedd4-2-mediated ubiquitination plays an important role in the downregulation of Na\textsubscript{V}1.5 in HF (Luo et al., 2017). SCN5A variants are now recognized to be involved in the pathogenesis of HF. A1180V, an SCN5A variant, decreased \textit{I}\textsubscript{Na-L} and moderately increased \textit{I}\textsubscript{Na-1.5}. A1180V carriers without cardiac dysfunction initially exhibit deteriorated cardiac functions and progress to HF or atrioventricular block during follow-up (Ge et al., 2008). Although some studies have elucidated the correlation between Na\textsubscript{V}1.5 and HF, the specific mechanisms are not yet known.

Considering the important role of Na\textsubscript{V}1.5 in these diseases, novel therapeutic strategies targeting the biosynthesis, trafficking, and sodium current of Na\textsubscript{V}1.5 have been developed.

Treatment Targeting Biosynthesis of Na\textsubscript{V}1.5

Several studies have proposed that promoting the process of translational readthrough can enable ribosomes to neglect the stop codon to produce full-length proteins and reduce the harmful results caused by nonsense mutations to a certain degree. Pharmacological strategies to enhance translational readthrough include aminoglycosides, small-interfering RNA (siRNA) that target eukaryotic release factors (eRF), and suppressor tRNAs that recognize stop codons (Carnes et al., 2003). This idea was tested in the nonsense mutation SCN5A-W822X by using aminoglycosides and siRNA against eRF3a and proved effective, which might be a novel treatment strategy for nonsense SCN5A mutation carriers (Teng et al., 2009). However, its application in clinical practice is largely limited due to safety concerns, such as introducing sequence changes to restored full-length proteins.

Treatment Targeting Trafficking of Na\textsubscript{V}1.5

H558R, a common SCN5A polymorphism, restores the defective trafficking of BrS-associated SCN5A mutations R282H, S216L, K317N, and D1690N by promoting proper protein folding (Marangoni et al., 2011; Shinlapawittayatorn et al., 2011; Nunez et al., 2013). The mechanisms by which H558R rescues SCN5A mutations are controversial. Decreased SCN5A promoter methylation by H588R is one of the mechanisms involved (Matsumura et al., 2017). In an \textit{in vitro} study, small peptides that span the H558R polymorphism, have been shown to be sufficient in restoring the trafficking defect of BrS-associated SCN5A mutations-R282H, indicating that it might be possible to use R558-containing peptides as a novel strategy tailored to specific BrS mutants (Shinlapawittayatorn et al., 2011). However, the rescue effects \textit{in vivo} still need to be investigated.

Treatment Targeting \textit{I}\textsubscript{Na-L} of Na\textsubscript{V}1.5

Ranolazine, eleclazine, amiodarone, mexiletine, flecainide, and quinidine targeting \textit{I}\textsubscript{Na-L} have been widely studied for the treatment of LQTS patients (Makielski, 2016). For example, we take mexiletine and ranolazine. Ranolazine, which is approved for the treatment of angina pectoris, preferentially reduces \textit{I}\textsubscript{Na-L}. To date, Ranolazine has been investigated with respect to SCN5A mutations such as ΔKPKQ, Y1767C, R1623Q, and D1790G (Moss et al., 2008; Rajamani et al., 2009; Huang et al., 2011; Chorin et al., 2016). Mexiletine, an oral class Ib anti-arrhythmic agent, targets cardiac Na\textsubscript{V}1.5, and preferentially inhibits \textit{I}\textsubscript{Na-1.5}. It has been reported that mexiletine can effectively shorten the QT interval in a subset of patients with LQT3, while other patients are insensitive to the drug (Mazzanti et al., 2016). The conformation of the less activated DIII voltage-sensing domain (DIII-VSD) of Na\textsubscript{V}1.5 is hypothesized to be the cause for mexiletine insensitivity in these patients (Zhu et al., 2019). A combination of mexiletine with a drug that can promote DIII-VSD activation can be a novel therapeutic strategy for these mexiletine-insensitive patients.

CONCLUSION AND PERSPECTIVES

The life cycle of Na\textsubscript{V}1.5 begins with the transcription and translation of the SCN5A gene. Na\textsubscript{V}1.5 is then trafficked from the ER to the Golgi apparatus and subsequently to the sarcolemma and cytoskeleton. Finally, Na\textsubscript{V}1.5 is internalized and degraded. In the past decades, great achievements have been made in the regulation of Na\textsubscript{V}1.5 from biosynthesis and trafficking to degradation. The knowledge we have generated helps in the understanding of the pathogenesis of SCN5A-related diseases and management of these patients. However, the complete life cycle of Na\textsubscript{V}1.5 has not been fully mapped. In the end of each section, we have pointed out the corresponding unsolved problems. All these problems can be summarized in two sections: regulation of Na\textsubscript{V}1.5 under physiological conditions and in pathological conditions. We believe that with joint efforts, we will achieve a deeper understanding of the life cycle of Na\textsubscript{V}1.5 and explore more effective treatment strategies to reduce mortality and improve the quality of life of patients suffering from SCN5A-related diseases.

AUTHOR CONTRIBUTIONS

CD and YW drafted the manuscript. AM and TW conceived and supervised the review. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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