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Abstract

Dravet syndrome is devastating infantile-onset epilepsy, often accompanied by severe intellectual disabilities, hyperactive behavior, autistic traits, and ataxia. The discovery in 2001 of the*SCN1A*mutation as a primary cause of this syndrome has accelerated our understanding of the pathophysiological processes underlying Dravet syndrome. *SCN1A* HQFRGHV WKH . VXEXQLW RI WKH YROWDJH-gated sodium channel Na$_V$1.1. Recent studies using genetically PRGL¿HG PRXVH PRGHOV KDYH LQGLFDWHG WKDW *SCN1A* defects in GABAergic inhibitory interneurons in the forebrain may be involved in the seizure susceptibility, fever sensitivity of seizures, premature death, and autistic traits characteristic of Dravet syndrome. More recently, human cellular models of Dravet syndrome have been established using patient-derived induced pluripotent stem cells (iPSCs) from three groups including ours. By taking advantage of these human disease models, functional vulnerabilities in GABAergic neurons have been revealed. Here, we review recent advances in Dravet syndrome research, particularly focusing on the development of iPSC models, and their future directions.

Keywords Epilepsy; -aminobutyric acid; Disease modeling; Genetics; Induced pluripotent stem cells; Mechanism; Mouse model; *SCN1A*

Abbreviation: DS: Dravet Syndrome; GABA: -amino Butyric Acid; iPSCs: Induced Pluripotent Stem Cells

Introduction

Dravet syndrome (DS)is a devastating epilepsy syndrome, which was rst described by Dr. Charlotte Dravet in 1978 [1]. Generalized or unilateral clonic seizures appear in previously healthy infants, and are frequently associated with fever [2]. ese seizures tend to evolve into status epilepticus and occur frequently especially during the early phases of DS. Other seizures, including focal, absence, and myoclonic seizures appear later. Seizures are refractory to most currently available treatments, and severe intellectual disabilities develop a er seizure onset, o en accompanied by hyperactive behavior and autistictraits. Ataxia worsens with age, resulting in signi cant gait disturbance. Furthermore, 10–20% of the a icted children experience premature death [3,4]. us, the development of new treatment is urgently needed.

Mutations in the*SCN1A*gene in patients with DS were rst reported in 2001[5]. Subsequent studies supported the hypothesis that the*SCN1A*defect is the primary cause of DS [6,7]; these ndings have triggered a number of studies attempting to uncover the pathogenic mechanisms underlying DS. ese studies have employed electrophysiological functional analysis of forcedly expressed Na$_V$1.1 mutants [8,9], mouse models based on heterozygotes of *SCN1A* knock-out/knock-in mouse [10,11], and more recently, human cellular models using patient-derived induced pluripotent stem cells (iPSCs) [12-14]. First, we brie y review previous research on DS and then describe our recent research on generating an iPSC model for DS.

Genetic alteration in*SCN1A*

*SCN1A*encodes the -subunit of the voltage-gated sodium channel Na$_V$1.1 (Figure 1) [15]. Abnormalities in the*SCN1A*gene were rst reported in patients with genetic epilepsy febrile seizures plus (GEFS+) [15], and have been also identi ed in patients with other clinical phenotypes, including cryptogenic focal/generalized epilepsies [16]. However, DS is the primary phenotype in which a robust correlation with *SCN1A* defects has been con rmed [17,18]: 70–80% of patients with DS carry*SCN1A*abnormalities [19,20].

Nearly 700 mutations in the*SCN1A*gene that are associated with DS have so far been identi ed [21], and most of them are *de novo*. ese mutations include nonsense, missense, splice site, and frameshi mutations, and are distributed throughout the gene. Speci c genotype–phenotype correlations remain unclear, but truncation mutations, harbored by half of the patients with DS, appear to be associated with a more severe phenotype than missense mutations [22]. Exonic or micro chromosomal deletions involving*SCN1A*or its promoter region have also been identi ed in patients with DS [23-27]. Other genes potentially associated with DS or similar phenotypes include *SCN1B* [28], *SCN2A* [29], *GABRG2* [30], and *PCDH19* [31,32]. However, mutations in the former three occur rarely, and only a minority of patients with *PCDH19* mutations present with the DS phenotype [33,34].

Functional alterations of mutated Na$_V$1.1

Electrophysiological studies examining the functions of mutated Na$_V$1.1 channels expressed in HEK293or tsA-201 cells have revealed that many of the DS-associated missense mutations result in an on functional sodium channel [8,9,35,36], and this loss-of-function of the channel may be associated with DS. One study revealed that expresse

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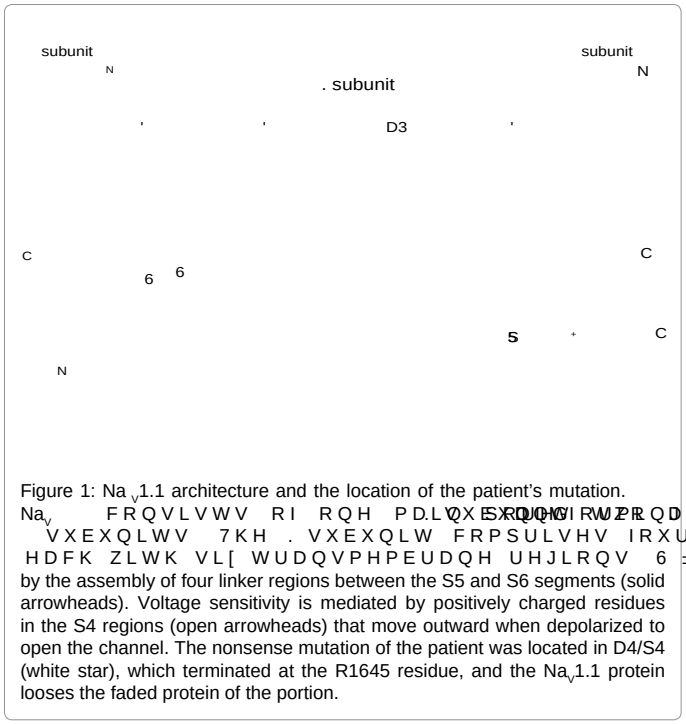

Figure 1: Na$_V$1.1 architecture and the location of the patient's mutation. Na$_V$ FRQVLVWV RI RQH PDLQ VXEXQLW RI WZR RU IRXU KRPRORJRXV GRPDLQV VXEXQLWV 7KH . VXEXQLW FRPSULVHV IRXU KRPRORJRXV GRPDLQV HDFK ZLWK VL[WUDQVPHPEUDQH UHJLRQV 6 ±6 by the assembly of four linker regions between the S5 and S6 segments (solid arrowheads). Voltage sensitivity is mediated by positively charged residues in the S4 regions (open arrowheads) that move outward when depolarized to open the channel. The nonsense mutation of the patient was located in D4/S4 (white star), which terminated at the R1645 residue, and the Na$_V$1.1 protein looses the faded protein of the portion.

truncated human Na$_V$1.1 (hNa$_V$1.1) did not a ect the channel function of co-expressed wild-type human hNa$_V$1.1, hNa$_V$1.2, hNa$_V$1.3, or hNa$_V$1.6 [37]. It is also true that SCN1A abnormalities in DS frequently include truncation mutations (mainly nonsense mutations) and gene deletions, while there is little evidence showing that the truncated hNa$_V$1.1 protein is expressed associated with nonsense mutation. Nonsense mutations of SCN1A gene could result in nonsense-mediated mRNA decay. Collectively, it is tempting to speculate that haplo insu ciency may be an underlying mechanism of DS. However, some missense mutations were found to induce gain-of-function of Na$_V$1.1 by way of activating sodium currents because of impairments in fast inactivation mechanisms [9]. It seems likely that the functional basis of SCN1A abnormalities related to DS may be more complex.

Dysfunction of GABAergic Interneurons in Mouse DS Models

Yu et al. rst reported a mouse DS model based on Scn1a knock-out in 2006 [10], which exhibited spontaneous seizures, temperature-dependent seizure susceptibility [38], and ataxia [39]. ey examined Na$_V$1.1 expression in the hippocampal GABAergic interneurons, and found a reduced sodium current density and impaired action potential generation in those neurons of Scn1a$^{+/-}$ and Scn1a$^{-/-}$ mice compared to wild-type mice, while these were normal in the pyramidal neurons. Reduced sodium current density was also con rmed in the Purkinje neurons of these animals [39]: this reduced current density may be involved in the ataxia associated with DS. Ogiwara et al. identi ed a parvalbumin-positive subgroup of GABAergic interneurons, which directly regulates the excitation of pyramidal neurons, as the primary type of Na$_V$1.1-expressing neurons in the neocortex and hippocampus [11]; moreover, intense Na$_V$1.1 expression was identi ed in their axon initial segments. e researchers generated Scn1a knock-in mice with the R1407* mutation, which exhibited spontaneous seizures, autistic traits, and cognitive decline [40], and impaired action potential generation in their neocortical GABAergic interneurons. ese heterozygous knock-out/knock-in mice were also prone to premature death [10,11].

Conditional SCN1Aknock-out, which was achieved by the Cre-mediated heterozygous deletion of oxed exonic regions, helped elucidate the brain region responsible for some of the major clinical features of DS [41]. Speci cally, Dlx1/2-enhancer-driven CredeletedScn1a in the mouse forebrain GABAergic interneurons [42]. ese mice exhibited spontaneous seizures, temperature-dependent seizure susceptibility, premature death, and autistic traits[43], as was observed in mice with global SCN1A deletion. Kalume, et al. made an extremely interesting observation regarding the mechanisms of sudden unexpected death during tonic–clonic seizures [44]: the mice that died had increased seizure frequency and ictal bradycardia, which could be ameliorated by atropine, suggesting that an increase in parasympathetic activity occurs. SCN1A knock-out in the heart did not a ect heart rate.

In the global knock-in and the conditional knock-out mice, administration of drugs that act to enhance GABAergic transmission, such as clonazepam, clobazam, or stiripentol ameliorated the seizures and behavioral impairments [43,45,46], supporting the notion that dysfunction of GABAergic interneurons is involved in the symptoms described above.

Human-Based Cellular Models for DS Developed Using Patient-Derived iPSCs

Generation of DS patient-derived iPSCs

Because it remains unclear whether mouse models faithfully reproduce the pathology occurring in the patient's brain, it is desirable to study patient's neurons directly. A er the development of human iPSCs by Yamanaka et al. in 2007 [47], many neurological diseases have been modeled using patient-derived iPSCs [48-53], and pathogenic alterations have been identi ed in their di erentiated neurons. Until recently, however, no such e ort has been reported for epilepsy.

We recently generated two lines of iPSCs (D1-1 and D1-6) from a female patient with a core DS phenotype, who harbors a nonsense mutation in SCN1A (p.R1645*, Figure1) [12]. Reprogramming factors (Sox2,Klf4, Oct3/4, and c-Myc) were retrovirally transduced into the skin broblasts, which were biopsied from her upper arm at the age of 29 years. e generated iPSCs displayed undi erentiated status and pluripotency, harbored the patient's mutation in their SCN1A gene, and could be e ciently and reliably di erentiated into neuronal cells. Neuronal di erentiation from the iPSCs was performed using a method established by Okada et al. [54] with a slight modi cation, in which a month of embryoid body formation is followed by 3–5 weeks of neurosphere formation. Terminal di erentiation into mature neurons was achieved by adherent culture of dissociated or undissociated neurosphere cells. For control experiments, we used 201B7, an iPSC line that was developed from a healthy female [47].

Functional Vulnerabilities in Patient iPSCs-Derived GABAergic Neurons

Because iPSCs-derived neurons obtained by the method described above are highly heterogeneous with regard to their neuronal subtypes and maturities, it is critical to analyze only one speci c type of neuronat a de ned level of maturity in order to determine whether the neurons are actually pathologic. As a rst step to overcoming these di culties, we generated a lentiviral reporter for SCN1A expression for electrophysiological assays; this harbors one main SCN1A promoter sequence [26], followed by a5′-untranslated exon

(to enhance expression speci city) [55], and Venus cDNA (Figure 2): 80–90% of the reporter Venus-positive neurons were Na$_V$1.1-positive. Moreover, immunocytochemistry revealed that>50% of Na$_V$1.1-positive neurons, and >70% of the reporter Venus-positive neurons were GABAergic (GAD67 (GABAergic neuron marker) and GABA-positive, respectively). VGlut1-positive (glutamatergic neuron marker) neurons appeared only rarely, and we could not evaluate their Na$_V$1.1 expression and functional properties su ciently. ese ndings indicate that the reporter detects Na$_V$1.1-positive GABAergic neurons with a high homogeneity.

Neuronal maturity is also critical for accurate functional assessment. For this purpose, we sought to improve the conditions for neuron selection in electrophysiological assays, and nally set the following requirements: 3–7 weeks (average, 30–45 days) of terminal di erentiation period; clear reporter uorescence; mature morphology (large cell body size and growth of 4 neurites); larger capacitance (30 pF); and more negative resting membrane potential (-30 mV). Using the current-clamp technique, the number and the amplitude of action potentials triggered by 500-ms depolarizing current injections were evaluated at various current intensities (input–output relationship). In the nal analyses, functionally immature neurons, which generated <10 action potentials during the stimulation protocol, were further omitted.

Although the capacitances, resting membrane potentials, ring thresholds, and peak voltages of action potentials were identical among the di erent cell lines, input–output relationships di ered when the injection currents intensi ed; there was a marked attenuation of both the amplitude and the number of evoked action potentials in patient's neurons compared to control neurons (Figure 3). ese ndings may indicate a reduced output capacity of the patient-derived neurons, particularly in the GABAergic subgroup, and are reminiscent of ndings from murine DS models [10,11].

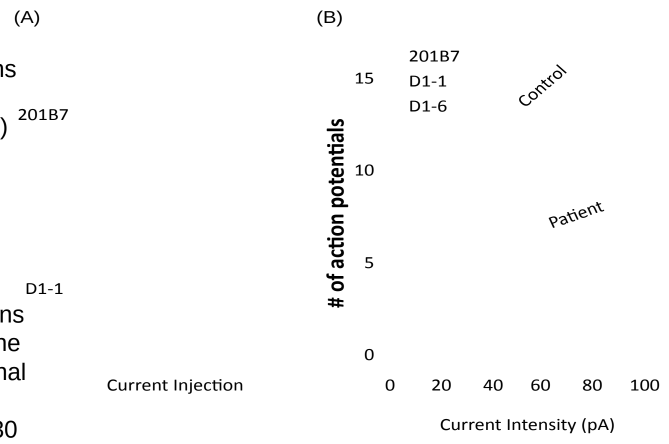

Figure 3: Representative traces of action potential trains and input-output relationships: DGDSWHG IURP 5HIHUHQFH > @ ZLWK PRG ms current injection period is indicated below. The traces presented are those evoked by a 100-pA current injection. Toward the end of the current injection, D1-1 neurons showed more prominent attenuation of action potential amplitude FRPSDUHG WR % QHXURQV DV LQGLFDWHG E\ WKH action potentials was also lower in D1-1. Scale bars indicate 20 mV and 100 ms. (B)Mean of the total number of action potentials evoked during the 500-ms VWLPXODWLRQ SHULRG YV LQMHFWLRQ FXUUHQW In all cell lines, the number of action potentials increased with intensifying currents. However, when current intensities exceeded60 pA, the rate of action potential increase plateaued in both patient lines, which was not the case in control cells.

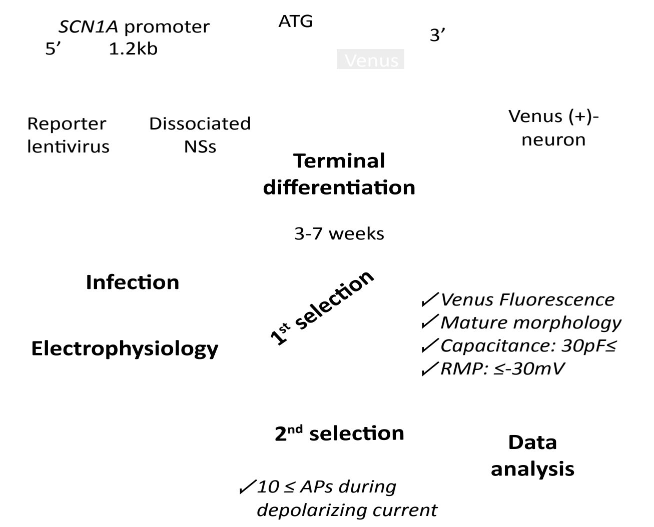

Figure 2: Diagram of the ***SCN1A*** reporter and neuron selection strategy for electrophysiological analyses: In the construct diagram, the yellow SRUWLRQ LQGLFDWHV WKH • XQWUDQVODWHG H[RQ WKH • XQWUDQVODWHG VHTXHQFH RI WKH ¿UVW transduced into the dissociated neurospheres by using lentiviral vectors. After ± ZHHNV RI WHUPLQDO GLIIHUHQWLDWLRQ SXWDWLYH VHYHUDO UHTXLUHPHQWV VHH PDLQ WH[W ZHUH DQDO\VLV)XQFWLRQDOO\ LPPDWXUH QHXURQV generation were excluded from analysis. APs, action potentials; RMP, resting membrane potential.

Hyperexcitability in DS iPSCs-Derived Neurons

Liu et al. also generated iPSCs from two patients with DS and di erentiated the cells into neurons by alternate methods [13]. e neurons were divided into two groups according to their morphology—bipolar or pyramidal—and their electrophysiological properties were evaluated. In both groups of neurons, the patients-derived lines showed lower ring thresholds, higher sodium current densities, and a higher rate of spontaneously bursting neurons than cell lines derived from controls, suggesting hyperexcitability of DS neurons. Most recently, Jiao et al. also con rmed the hyperexcitability in excitatory neurons derived from DS patient-iPSCs [14]. Although such ndings on the hyper excitability were not con rmed in our preliminary experiments (Higurashi et al., unpublished results), they provided a novel gain-of-function hypothesis for the mechanisms underlying seizure susceptibility in DS, which have not been revealed by murine research. Further development of the iPSC research technique will be necessary to elucidate the precise mechanisms involved.

Future Directions of DS Research Using Patient-Derived iPSCs

Disease modeling with patient-derived iPSCs has just begun, particularly in the eld of epilepsy. Although the results of these two iPSC studies on DS are not immediately bene cial for patient treatment, they strongly indicate the utility of the new platform for human epilepsy research. In the next step, re nement of the culture technique and a more cell-type-speci c analysis for various types of neurons (e.g. glutamatergic, parvalbumin-positive GABAergic, calretinin-positive GABAergic, and somatostatin-positive GABAergic, etc) will be necessary. e continued use of mouse models to con rm our ndings

from iPSCs will facilitate the elucidation of key pathophysiological mechanisms and critical therapeutic targets in human patients with DS.

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