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EDITORIAL

Ion channelopathies to bridge molecular lesions, channel function, and clinical therapies

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The advent and rapid expansion of disease-associated channelopathies

Ion channels regulate ion fluxes across cell membranes. They are present in the membranes of all animal, plant, and bacterial cells and play key roles in all the major aspects of cell development and function. Ion channels are expressed in different proportions and densities depending on the role they play to effectively regulate cell function at rest and during activity. As such, they are important contributors of cellular homeostasis and have vital role in epithelial transport, endocrine function, contractility, and neuronal excitability. Defects in ion channel activity either inherited or acquired may have therefore profound physiological effects on cell and tissue functions, often leading to severe clinical disorders.

The notion that human disorders may arise from a heritable defect in ion channel genes (channelopathies) is a well-established concept since the early 1970s, when neurophysiologists were studying the reasons of several disorders in skeletal muscle excitability (myotonia and periodic paralysis) [1]. Extensive electrophysiological and genetic studies in the following 15 years, on patients affected by hyperkalemic periodic paralysis, could clearly show that in this rare dominant disease, the inactivation of skeletal muscle sodium channels (Nav1.4) was defective [34, 35] and that the disorder was associated with mutations on the SCN4A gene [48]. This latter study by Rojas et al. is now considered the first report to identify a voltage-gated ion channelopathy (see [27] for a review). Subsequently, a series of studies on muscle disorders in humans and mice uncovered new dominant genetic defects of the α1 subunit of Cav1.1 skeletal muscle Ca^{2+} channels (hypokalemic periodic paralysis; [30]) and the two pores ClC-1 Cl^- channels (Becker's and Thomsen's myotonia; [32]). Since then, the list of inherited or de novo mutations has rapidly expanded and now includes channelopathies of most K^+ [15, 23, 50], Na^+ (Nav1.9) [29, 59, 60], Ca^{2+} (Cav1.4, Cav2.2, Cav2.3) [8, 41, 64], TRP [39, 58], HCN [19, 52], and Cl^- channels [38, 46, 47]. Disease-associated mutations have been identified also for several fast ligand-gated receptors or channels (nAChR, NMDAR, glycine receptor, $GABA_AR$), for intracellular channels (ryanodine receptor), and for intercellular channels (connexins), which are summarized in several excellent reviews [2, 7, 9, 20, 25, 53, 65] and books [3]. All these channelopathies are now recognized to affect a wide range of organs and to represent a substantial disease burden [11].

Limiting the focus on channelopathies dysregulating functions of excitable cells, these disorders have grown nowadays to a large number. They now include a heterogeneous group of inherited disturbances such as muscle membrane excitability disorders (myotonias and various forms of periodic paralysis), certain forms of cardiac dysfunction (Brugada syndrome, long and short QT syndromes, atrial and ventricular fibrillations), some forms of epilepsy, episodic ataxias, and some inherited pain syndromes (inherited erythromelalgia, paroxysmal extreme pain disorder) [31, 33].

More recently, the expansion of knowledge on channelopathies has been dramatically accelerated. This is due to the increasing number of groups interested in disease-associated channel variants and the increasing number of worldwide clinical screenings vigorously performed on numerous patients affected by a specific disease in association with large-scale next generation sequencing (NGS) studies that allow unprecedented new insights in the identification of rare disease-causing variants. In addition to the large number of already identified channelopathies associated with dominant or recessive inherited defects, large-scale NGS studies allow

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researchers to uncover an increasing number of ion channel de novo mutations (missense, nonsense, frameshifts, in-frame deletion) that widen enormously the possible channel variants associated with a specific pathology.

A key issue for neurophysiologists and neuropharmacologists is to determine whether a specific mutation causes a loss of function (LOF) or a gain of function (GOF) of ion activity (gating, permeability, membrane trafficking, degree of channel expression) and, importantly, how LOF or GOF interfere with cell function to produce neuronal, muscular, or endocrinal disorders [33]. It is interesting, for instance, that most LOF of Nav1.1 sodium channel variants are associated with the sporadic epilepsy disorder SMEI (severe myoclonic epilepsy of infancy or Dravet's syndrome) [12], while GOF variants of Cav1.2 and Cav1.3 calcium channels are associated with different forms of autism spectrum disorders [10, 45, 55]. In the case of SMEI, half of more than 600 identified de novo Nav1.1 mutations are due to stop codons or in-frame deletions that cause reduced expression of Nav1.1, while a large number are Nav1.1 missense mutations concentrated in the transmembrane segments of the protein, where they prevent channel expression or severely impair channel function. In the case of Cav1.2 and Cav1.3 channels, the GOF causing autism or intellectual disabilities is associated with a "negative shift" of voltage-dependent activation and steady-state inactivation that increases the resting window Ca^{2+} current [10, 26, 45]. Two other interesting examples on how GOF and LOF could differently affect human disorders come from the Nav1.7 and Nav1.9 sodium channels widely expressed in peripheral sensory neurons. In the case of Nav1.7, GOF variants cause severe painful disorders (inherited erythromelalgia (IEM) and paroxysmal extreme pain disorder (PEPD)), while LOF variants cause congenital insensitivity to pain (CIP) [60]. In the case of Nav1.9, there is evidence only for GOF missense mutations [16], but it is interesting that while most Nav1.9 mutations lead to painful conditions, there are few missense GOF mutations causing CIP [36], in an apparently conflicting situation compared with CIPs induced by Nav1.7 LOF.

A special issue on amazingly interesting new insights on ion channelopathies

The field of channelopathies has greatly progressed in the last 10 years. This is firstly due to the improved single-particle cryo-EM technique that allows solving the structure of numerous transmembrane ion channels (TRP, Na^+, K^+, Ca^{2+}, Cl^-) at impressive high resolution (~3 Å) [14, 43, 54, 57, 62]. A second further advancement on channelopathies comes from the various genome-wide association studies (GWAS) as well as exome sequencing studies that in the last years have contributed in identifying risk genes for neurological disorders and disease mutations. A third recent improvement comes from the availability of new knock-in mice bearing human ion channel mutations that mimic human disorders and can be effectively used to study how channel mutations alter body function at the cellular, tissue, and organ level. All this has made an extensive amount of new information accessible that helps better understanding the altered molecular and cellular mechanisms induced by channelopathies. In this special issue, we present a selected paper contribution of ion channel physiologists, pharmacologists, and molecular biologists who report recent advances on channelopathies of Ca^{2+}, Na^+, K^+, Cl^-, TRP, and HCN channels linked to human disorders of excitable cells.

Cav channels

A large group of reviews is dedicated to classical and newly discovered channelopathies of voltage-gated Ca^{2+} channel (Cav). Cav channels form a family of 10 different isoforms classified into high-voltage (Cav1.1–1.4, Cav2.1–2.3) and low-voltage–activated (Cav3.1–3.3) channels. They are expressed at different proportions in nearly all excitable cells and control neuronal excitability, synaptic plasticity, gene transcription, muscle contraction, cardiac automaticity, and hormone release. Regarding the Cav1.1 L-type Ca^{2+} channel isoform specifically expressed in skeletal muscles, a detailed review by *Flucher* describes recently reported channelopathies modulating excitation-contraction (EC) coupling in humans. The specific emphasis is on the four types of inherited skeletal muscle diseases linked to mutations in the *CACNA1S* gene (hypo- and normokalemic periodic paralysis, malignant hyperthermia susceptibility (MHS), Cav1.1-related myopathies, and myotonic dystrophy type 1 (DM1)) and the mutation in the Cav1.1-associated protein STAC3 causing Native American myopathy (NAM) [28]. GOF mechanisms causing either excessive Ca^{2+} influx through misspliced Cav1.1 or hypersensitive release of Ca^{2+} by RyR1 are the likely causes of DM1 and MHS, while a loss of the EC coupling interactions between Cav1.1 and RyR1 [61] appears to be the first step in the patho-mechanism of NAM.

The identification of rare disease-causing variants in humans by GWAS also provides new insights into the pathophysiological role of de novo missense variants in the *CACNA1D* gene that encodes the pore-forming α1 subunit of voltage-gated Cav1.3 L-type channels. Cav1.3 is effective in the auditory, cardiac, endocrine, and nervous system. In this issue, *Ortner* et al. discuss in great details classical and newly uncovered *CACNA1D* variants identified somatically in aldosterone-producing adenomas (APA) and germline in patients with neurodevelopmental and endocrine symptoms [45]. They show how in vitro studies in heterologous expression systems reveal typical gating changes that cause enhanced Ca^{2+} influx through mutated Cav1.3 channels as the

underlying disease-causing mechanism [26]. The authors summarize the clinical findings of 12 well-characterized individuals with autism and/or development delay with 9 high-risk pathogenic *CACNA1D* variants. They also propose how information from somatic mutations in APA can be used to predict the potential pathogenicity of novel germline variants.

Similar to Cav1.3, Cav1.2 L-type Ca^{2+} channels play key roles in long-term synaptic plasticity, sensory transduction, muscle contraction, and hormone release. De novo mutations in the gene encoding Cav1.2 (*CACNA1C gene*) cause two forms of Timothy syndrome (TS1, TS2), a multisystem disorder causing cardiac arrhythmias, long QT, autism, and adrenal gland dysfunction [56]. Trying to identify the molecular basis of Cav1.2 gating dysfunctions leading to autism, in this issue, *Marcantoni* et al. discuss the properties of recently reported typical and atypical TS phenotypes that cause specific GOF changes to Cav1.2 channel gating [10, 17]. They also discuss new emerging findings using iPSC-induced neurons [42] and the newly available autistic TS2-neo mouse model [4], both appearing promising for understanding neuronal mistuning in autistic TS patients.

Given the critical role of Cav2.1 P/Q-type channels (*CACNA1A gene)* in controlling neurotransmission in excitatory and inhibitory central synapses, the channelopathies of the α1 subunit of Cav2.1 cause multiple neurological disorders including sporadic, familial hemiplegic migraine, and cerebellar pathologies such as episodic ataxia, progressive ataxia, and congenital ataxia (CA). In this issue, *Izquierdo-Serra* et al. describe the increasing number of *CACNA1A* genetic variants linked to CA in the context of Ca^{2+} homeostasis alteration. They describe each pathological mutation according to structural location and known molecular and cellular functional effects in both heterologous expression systems and animal models. The issue contains also a short review by *Toni Schneider* on the recently reported de novo mutations of the Cav2.3 R-type calcium channel that cause developmental and epileptic encephalopathy [24]. So far, no inherited diseases are known about Cav2.3, but given the key role of the channels in contributing to central neurotransmission, the channelopathies of *CACNA1E* gene are expected to cause severe brain pathologies. It is interesting that most of the Cav2.3 GOF mutations occur in the four 6S segments of the pore-forming α1 subunit of the channel that controls channel activation. S6 GOF variants are common to de novo mutations of Cav1.2 (*Marcantoni* et al. in this issue), Cav1.3 (*Ortner* et al. in this issue) and Cav3.1 (*Lory* et al. in this issue), all leading to intellectual disabilities.

Cav3.1 together with Cav3.2 and Cav3.3 belongs to the low-voltage–activated T-type Ca^{2+} channel family and is involved in a wide variety of physiological functions, especially in the nervous system and heart. Their unique electrophysiological properties allow them to finely regulate neuronal excitability and to contribute to sensory processing, cardiac beating, sleep, and hormone and neurotransmitter release [40]. Mutations in the genes encoding the Cav3 channels (*CACNA1G, CACNA1H, CACNA1I*) have been linked to a variety of neurodevelopmental, neurological, and psychiatric diseases designated as neuronal Cav3 channelopathies. In this issue, *Lory* et al. describe and discuss the clinical findings and the supporting in vitro and in vivo studies of the mutant channels, with a focus on de novo and GOF missense mutations recently discovered in *CACNA1G* [13] and *CACNA1H* [63]. T-type Cav3.1 and L-type Cav1.3 and Ca^{2+} channels play also important roles in the spontaneous activity of cardiac pacemaker cells. In this issue, *Torrente* et al. discuss rare forms of inherited and autoimmune channelopathies affecting Cav1.3 and Cav3.1 channels. These channelopathies specifically disrupt cardiac pacemaker activity and impulse conduction through the heart chambers. Recent research on familial disease has identified mutations in the Cav1.3-encoding *CACNA1D* gene that underlies congenital sinus node dysfunction and deafness [5]. The discovery of channelopathies linked to Cav1.3 and Cav3.1 channels underscores the importance of Ca^{2+} channels in the generation and regulation of heart's automaticity. A final review on auxiliary Cav channel subunits regards the emerging field of channelopathies associated with the α2δ regulatory subunits of Cav channels. α2δ proteins are abundantly expressed in the brain and the peripheral nervous system and regulate pre- and postsynaptic functions. Recently, the human genes (*CACNA2D1–4*) encoding for the four known α2δ proteins (isoforms α2δ-1 to α2δ-4) have been linked to a large variety of neurological and neuropsychiatric disorders including epilepsy, autism spectrum disorders, bipolar disorders, schizophrenia, and depressive disorders [21]. In this issue, *Ablinger* et al. provide an overview of the hitherto identified disease associations of all known α2δ genes, hypothesize on the pathophysiological mechanisms considering the known physiological roles of α2δ subunits, and discuss the most immanent future research questions.

Na^+ and K^+ channels

This special issue contains also updated reviews on newly discovered Na^+ and K^+ channelopathies. Regarding Nav channels, *Baker and Nassar* focus on the critical roles that Nav1.7 (*SCN9A* gene) and Nav1.9 (*SCN11A* gene) channels play in pain signaling in human channelopathies. GOF mutations in *SCN9A* cause painful conditions in contrast to LOF mutations responsible for CIP has been already defined above [60]. With regard to Nav1.9 channels, there is evidence only for GOF mutations [16], but it is interesting that while most *SCN11A* mutations lead to painful conditions, a few recently reported mutations cause CIP [36]. Strikingly, all CIP mutations are located at the end of the S6 segments and cause markedly negative shifts to Nav1.9 channel activation. Regarding Kv channels, *Nappi* et al. give a review on the

genetically determined epileptic channelopathies affecting Kv7.2 (*KCNQ2*), Kv7.3 (*KCNQ3*), and Kv7.5 (KCNQ5) channels. The authors review the phenotypic spectrum of Kv7-related epileptic channelopathies, the different genetic and pathogenetic mechanisms, and the emerging genotype-phenotype correlations that may prove crucial for prognostic predictions, disease management, parental counseling, and individually tailored therapeutic attempts. The second report on Kv channelopathies by *Hasan* et al. considers Kv1.1 variants responsible for episodic ataxia 1. The authors show that replacement of glycine 311 with aspartate in the S4–S5 linker of Kv1.1 channel induces drastic changes to the voltage-dependent electromechanical coupling of channel gating.

To give a broader view of the channelopathies affecting the vast family of K^+ channels, two reports in this issue describe the channelopathies of TWIK-related K^+ channels. The article by *Inoue* et al. describes the relatively few LOF mutations of TWIK-related acid-sensitive K^+ (TASK) channels that contribute to the resting membrane potential in different types of cells, such as brain neurons, smooth muscle cells, and endocrine cells. LOF missense mutations in the *KCNK3* gene encoding for TASK1 channels are one of the causes of pulmonary hypertension in humans [37], whereas the inherited missense LOF mutation reported for TASK3 channels (*KCNK9* gene) results in a syndrome of mental retardation, hypotonia, and facial dysmorphism [6]. No GOF mutations are reported so far for TASK channels. The report by *Imbrici* et al. focuses on a new inherited missense variant of TWIK-related spinal cord K+ channel (TRESK), specifically on the LOF W101R mutation in the *KCNK18* gene that is diagnosed in a patient with intellectual disability and migraine with brainstem aura [22]. The variant causes a dramatic loss of TRESK channel function as well as an initial dominant-negative effect when co-expressed with wild-type channels in *Xenopus* oocytes.

HCN and TRP channels

To complete our overview on channelopathies, the special issue includes three updated reviews on HCN, TRP, and skeletal muscle ClC-1 channelopathies and one review on the "neuron-specific" K^+ Cl^- co-transporter 2 (KCC2) pathologies. Regarding cardiac and neuronal HCN1–4 channelopathies, *Rivolta* et al. provide a detailed description of the severe cardiac and neurological dysfunctions associated with an increasing number of HCN channel variants. Mutations in HCN4 are typically associated with sinus node dysfunction, atrial fibrillation, ventricular tachycardia, and atrioventricular block [18], whereas mutations in neuronal HCN1, HCN2, and HCN4 are associated with various forms of epilepsy, Parkinson's disease, and neuropathic pain [51]. Regarding TRP channels, *Naert* et al. briefly review the current knowledge on the TRP channelopathies, re-evaluating some available functional data and pointing out the aspects that require attention in future research. The authors make emphasis on the human TRPA1 channel, which exhibits a GOF mutation associated with the rare familial episodic pain syndrome and other mutations linked to altered chemosensation. They also discuss a unique opportunity for further developments provided by combining recently resolved cryo-EM structure of TRPA1 [44] that provides a unique opportunity for further developments, in combination with classical electrophysiology and analysis of channel gating.

Cl^- channels

The issue includes also an updated report by *Altamura* et al. on the advancement in understanding the role of ClC-1 channels in skeletal muscle and the wide spectrum of pathophysiological conditions associated with modification of ClC-1 activity leading to congenital myotonia. Starting from the recently resolved cryo-EM structure [43], the review summarizes the most relevant research on ClC-1 channel physiology, associated diseases, and pharmacology. Importantly, the studies on ClC-1 channelopathies support the idea that ClC-1 is relevant to preserve excitability but also for adaptation to physiological or harmful events in skeletal muscle. Associated with Cl^- channel functions, the issue contains also a review on the "neuron-specific" K^+-Cl^- co-transporter 2 (*KCC2*). Based on the previous reports [49] and more recent findings, *Akita and Fukuda* discuss how genetic mutations in human KCC2 cause infantile migrating focal seizures caused by $[Cl^-]_i$ dysregulation. The authors also propose a new mechanism (the "unifying foci" model) by which brain insults or *KCC2* mutations cause Cl^- imbalance in neurons leading to epileptic discharges.

Conclusions and future perspectives

As pointed out in this special issue, we begin to understand several clinical disorders associated with some of the inherited and de novo channel variants. This is because of the progressively increasing number of newly identified channelopathies and a better understanding of channel structure and function. It is very likely that channelopathies will expand more in the future and will cover a large part of ion channel pathophysiology. This is certainly beneficial for better understanding the molecular origins of many disorders and for providing clinicians with an accurate molecular diagnosis of the different diseases to develop new effective therapies. Improvements in this field are expected from a better resolution of the 3D structure of ion channel by the cryo-EM technique, the use of iPSCs to generate mutated cell populations with incorporated channel variants derived from patients, and the use of genetically engineered mice that recapitulate human disorders. But,

particularly for the de novo mutations affecting young individuals, improvements will depend on the support of the families of patients and their willingness to collaborate with clinicians and the scientific community in a responsive manner that goes beyond clinical routine.

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