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EDITORIAL

RECENT INSIGHTS INTO CHANNELOPATHIES

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1. INTRODUCTION

The membrane of cells and intracellular organelles is composed of two layers of lipids, preventing the free "in and out" movement of water and solutes that are necessary for proper cell and organelle function. This movement is then facilitated by the presence of specialized integral membrane proteins that we categorize as channels, pumps, and transporters. Because of the multitude of ions and organic molecules that necessitate transport across biological membranes, there are hundreds of proteins (derived from hundreds of genes) fulfilling this function. Disruption of a single gene or protein function can have devastating consequences for the survival of an organism. Many human diseases are linked to deleterious mutations in membrane proteins. A priori, there is no reason to distinguish the diseases that are caused by channels versus those caused by pumps and transporters. The biology behind functional defects of membrane proteins, such as loss of function, gain of function, trafficking defects, etc., is shared among all proteins, irrespective of their classification (**FIGURE 1**). As a matter of fact, the same disease, although maybe with some unique features, might be caused by a deficit in a channel or in a transporter. This is the case for Bartter syndrome, which is caused by inactivating mutations in genes encoding the Na-K-2Cl cotransporter-2 NKCC2 (type 1), the K^+ channel ROMK (type 2), the Cl^- channels CLCNKA and CLCNKB (type 3 and 4 b), and barttin, a β-subunit of the CLCNK channels (type 4a). However, scientists love to create categories, and therefore disorders caused specifically by disruptions in ion channels are known as channelopathies. This term was first used in a publication title in 1993, in reference to a hyperkalemic periodic paralysis disorder caused by a sodium channel gene (1). Thus, in 2023, we reached 30 years of research on diseases caused by defects in ion channels, and with the classification caveat stated above, we thought it useful to reflect on the topic. In addition, as the cost of genome sequencing has dropped significantly in the past two decades ($1,000,000 in 2007 to ∼$600 today), whole exome sequencing of patient DNA has become somewhat routine, and this has led to the identification of new mutations. These mutations are not inherited or associated with family pedigrees, but they are rather novel or "de novo" mutations that arose during meiosis or early embryonic development and therefore became part of the genetic makeup of a diseased individual (2). It is important to note that even if the origin of these mutations is different, they are otherwise not intrinsically different in the ways they affect channel function. Although we are not covering de novo mutations in depth here, the rise in their numbers will provide additional insights into channelopathy mechanisms of (3–5).

Since this is an editorial and not a review article, we cannot be comprehensive and discuss all channels involved in diseases, including some of the well-studied channelopathies. We have instead picked a few channels and diseases representative of some of the major substrates. We also note that a series of excellent reviews on ion channels and channelopathies were published in the past few years in *Physiological Reviews* and in other American Physiological Society (APS) journals, and those contributions are highlighted in this editorial.

2. CLASSIFICATION FROM SUBSTRATES

2.1. Cl^- Channelopathies

The first Cl^- channelopathy involved the cloning, identification, and characterization of the cystic fibrosis gene (6). Cystic fibrosis (CF) is a devastating disease that affects the lungs, pancreas, sweat glands, and vas deferens. Before the identification of the channel encoded by the CF gene, it was known that the basic defect was

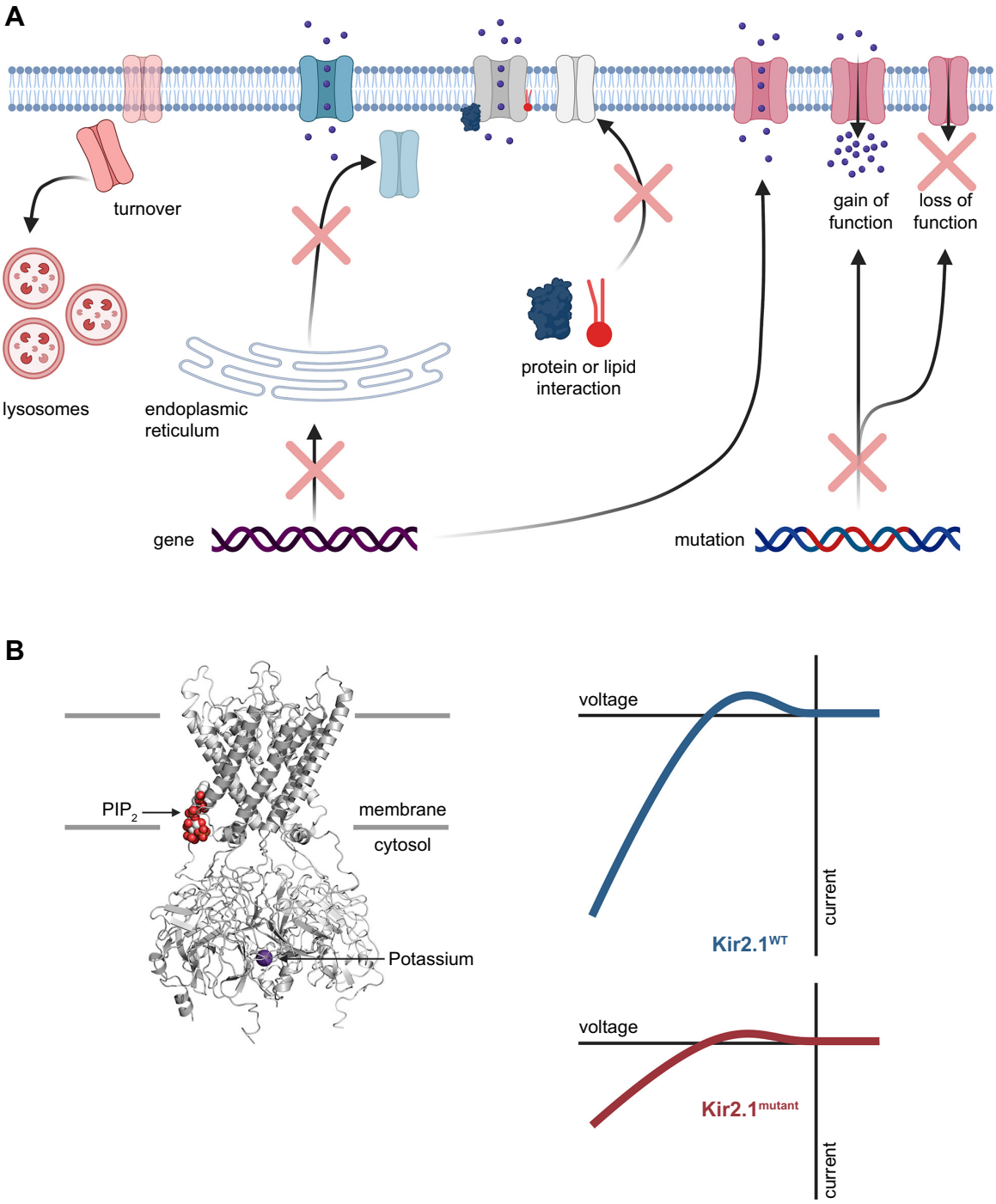

FIGURE 1. Channelopathies. *A*: possible molecular mechanisms leading to ion channel dysfunction include transcription or trafficking defects, loss-of-function or gain-of-function of the channel itself, defect in recycling/degradation, and abnormal protein or lipid interactions. *B*, *left*: model of Kir2.1 drawn from the cryogenic electron microscopy tetrameric structure of the human channel protein (PDB: 7ZDZ). The model shows the interaction of one chain with phosphatidylinositol-4,5-bisphosphate (PIP_2). *B*, *right*: hypothetical traces reflecting wild-type (blue) and mutant Kir2.1 channel (red) activities. Figure was made with BioRender.com with permission.

associated with decreased chloride conductance across the apical membrane of epithelial cells. Upon cloning, the protein was not originally recognized as a chloride channel but as a regulator of chloride conductance. Irrespective, the cloning made it clear that the cystic fibrosis transmembrane conductance regulator (CFTR) protein was defective in cystic fibrosis. A 3-bp deletion resulting in the absence of a phenylalanine residue (ΔF508) was detected in 68% of chromosomes carrying a CF mutation, while 0/198 chromosomes from normal individuals carried the mutation (6). Following this original report, some 13,000 papers were published, making

CFTR the most studied channelopathy in human medicine. This channelopathy is interesting in two respects. First, CFTR is the most common monogenic disorder in Northern European whites, with a carrier frequency of 1 in 24/25 and a birth prevalence of 1 in 2,500. This leads to a population of ~105,000 patients worldwide. The prevalence of carriers led to the hypothesis that the ΔF508 mutation might have had a selective advantage, like the protection that sickle cell anemia might have against malaria (7). Second, the loss of this key residue does not lead to an intrinsic loss of channel activity, but a loss of membrane expression due to a trafficking defect (**FIGURE 1**) (8, 9). Because of this unique property, drugs have been designed to facilitate the trafficking of ΔF508 to the plasma membrane, thereby rescuing function and helping CF patients (10). Note that these agents can also correct other protein trafficking diseases (10).

Another Cl^- channelopathy affects skeletal muscle, rather than epithelial cells. In the late 1800s, a few goats in Tennessee displayed an unusual "fainting" phenotype. During a 5- to 20-s crisis episode, the animal experienced complete paralysis and stiffness of its skeletal muscles leading to an immobility that is associated with a fall. This fainting was first described in the scientific literature in 1904 (11) and referred to as a congenital myotonia in 1939 (12). An alanine to proline substitution at the COOH-terminal tail of ClC-1 chloride channel was discovered in 1996 at Vanderbilt University (13). Around the time the goats were discovered and became a curiosity, Dr. Asmus Julius Thomsen in Denmark reported an inheritable condition of delayed relaxation of skeletal muscle following severe contraction (14). The first cases of autosomal dominant myotonia congenita were reported to be due to a glycine to glutamic acid substitution in an extracellular loop of the ClC-1 channel (15).

The examples provided above are just the tip of the iceberg. There are over 50 genes encoding Cl^- channels, most of which participate in critical functions in the body. Examples of disease states associated with mutations in chloride channels are as follows: hyperaldosteronism [ClC-2 (16)], Dent's disease [ClC-5 (17)], osteopetrosis [ClC-7 (18)], Deafness and Bartter syndrome [ClC-Kb (19) and Barttin (20)], retinal disease [bestrophin (21)], and epilepsy [GABA receptor (22)]. These examples, and many others, also emphasize that ion channel expression determines phenotype. Some channelopathies, Cl^- or others, demonstrate defined pathology due to restricted channel expression or compensatory mechanisms in unaffected organs. Other channelopathies, however, affect several organs due to the wide expression of defective channels.

2.2. Na^+ Channelopathies

A significant number of sodium channelopathies affect the cardiac muscle and heart function. The primary voltage-gated sodium channel expressed in cardiac myocytes is Nav1.5. Encoded by *SCN5A*, Nav1.5 is an essential modulator of cardiac excitability. Nav1.5 expression at the cardiomyocyte membranes is particularly enriched at the intercalated disks so that decreased channel trafficking and expression at the plasma membrane leads to reduced Na^+ current and arrhythmogenic cardiomyopathy (23). The etiology of cardiac Nav1.5 dysfunction is either inherited, due to hundreds of *SCN5A* mutations (e.g., congenital long-QT syndrome, Brugada syndrome, arrhythmogenic cardiomyopathy), or acquired due to cardiac disease.

Interactions between Nav1.5 and other proteins that are heterogeneously enriched underlie subcellular modulation of Na^+ channel activity (24). Given that Nav1.5 forms complexes with interacting proteins, Nav1.5 channelopathies leading to cardiac disorders could be attributed to mutations in genes other than *SCN5A*. Mutations of genes encoding β-subunits of Nav channel reduce Nav1.5 activity and are linked to sudden cardiac death in Brugada syndrome and sudden infant death syndrome (24). To summarize, cardiac sodium channels are among the most affected by channelopathies, either due to mutations in the gene encoding the sodium channel or in the genes encoding proteins that interact with sodium channels (**FIGURE 1**).

Many voltage-gated Na^+ channels, other than Nav1.5, are involved in human diseases. Mutations in Nav1.1, 1.2, and 1.3 channels that are expressed in the central nervous system lead to developmental epileptic encephalopathies, epilepsies, and migraines (25). Mutations in Nav1.4 affect muscle health (26), leading to myotonia and periodic paralysis, and mutations in the peripheral nerves Nav1.7-1.8 channels lead to neuropathies and pain perception disorders (27).

The epithelial sodium channel (ENaC) is expressed at the apical membrane of a variety of epithelial cells where it moves Na^+ from the lumen into the cells for the basolateral Na^+-K^+-ATPase to pump it into the interstitium. The channel is expressed in the distal nephron of the kidney where it participates in the reabsorption of 5% of the filtered Na^+ (28), in the lung where it clears alveolar fluid (29), in the gut where it contributes to intestinal salt reabsorption (30), and in the vasculature where it transduces mechanical stimuli (31), just to cite a few tissues from a larger list. The channel is composed of α-, β-, and γ-subunits. Heterozygous mutations in *SCNN1A*, *SCNN1B,* and *SCNN1G*, encoding α-, β-, and γ-subunits, respectively, result in Liddle syndrome that is characterized by early onset salt-sensitive hypertension, hypokalemia, metabolic

alkalosis, and suppression of plasma renin activity and aldosterone secretion (32). The clinical presentations are compatible with a gain-of-function of the channel. In 1995, Snyder and colleagues (33) identified a motif in the carboxyl-terminal tails of the β- and γ-subunits, that when mutated results in increased ENaC cell surface expression. This motif is absent in truncated mutants of β- and γ-subunits associated with Liddle syndrome. Opposite to Liddle syndrome is pseudohypoaldosteronism type 1 (PHA1) where loss-of-function mutations in ENaC subunit genes lead to salt wasting and high concentrations of sodium in sweat, stool, and saliva. Mutations in the mineralocorticoid receptor gene that regulates ENaC expression also lead to PHA1 (34). Thus, depending on the type of disruption/mechanism of disease, ENaC disruption leads to different channelopathies.

2.3. K^+ Channelopathies

Potassium (K^+) channels are ubiquitously expressed and play crucial roles in the regulation of membrane potential and cell excitability. One of the K^+ channel classes that is prone to channelopathies is the inwardly rectifying (Kir) K^+ channels. It is timely that the *American Journal of Physiology – Cell Physiology* recently published a series of review articles dedicated to Kir channel physiology and pathophysiology (35). A well-characterized channelopathy affects the strong inwardly rectifying Kir2.1 channel. Mutations of *KCNJ2,* encoding Kir2.1, cause the Andersen-Tawil syndrome in which dominant mutation carriers suffer from cardiac arrhythmias, skeletal muscle weakness (periodic paralysis), and craniofacial and cognitive abnormalities (36–38). Mechanistic studies into the etiology of the Andersen-Tawil syndrome unraveled several *KCNJ2* mutations that perturb the interaction between the channel and the phosphoinositide phosphatidylinositol-4,5-bisphosphate (PIP_2) (39, 40). The latter, PIP_2, is a cofactor that is crucial and indispensable for Kir2.1 activation (**FIGURE 1**). Building on the original observations 25 years ago that PIP_2 is necessary for Kir2.1 activity (41), structural analyses confirmed that PIP_2 binds to the channel at sites that have been linked to pathogenesis (42).

While Andersen-Tawil syndrome's symptoms predominantly impact the heart and skeletal muscles, recent studies have further demonstrated an important role for the channel in blood flow control in the brain (43). Increases in external K^+ concentrations ($[K^+]_{ex}$) in the cerebral circulation have been long linked to blood flow increases (44). Importantly, the Kir2.1 channel conductance increases profoundly in response to small elevations in $[K^+]_{ex}$. Recent evidence suggests that extracellular K^+, a byproduct of neural activity (45), increases local blood flow to active brain regions in a Kir2.1-dependent manner (43). In line with the indispensability of PIP_2 for Kir2.1 function (**FIGURE 1**), the ability of vascular Kir2.1 to sustain blood flow increases relies on PIP_2 availability (46). Several studies have discovered vascular Kir2.1 channelopathies that are attributed to the unavailability of the cofactor PIP_2 in neurodegenerative and small vessel diseases (47–49).

PIP_2 is a crucial and versatile signaling molecule, and therefore, its dysregulation is implicated in several diseases. PIP_2 metabolism, for example, is dysregulated during Alzheimer's disease (50, 51). Channelopathies due to compromised PIP_2-ion channel interaction apply not only to K^+ channels but to ion channels in general (52). This stresses that channelopathies could be caused by inherited changes in the channel itself or by acquired alterations in channel activity. Altered channel expression and disrupted channel regulation are possible changes leading to a channelopathy of a nonmutant channel (**FIGURE 1**).

2.4. Ca^{2+} Channelopathies

The most abundant second messenger in cellular signal transduction is calcium. Mechanisms involved in Ca^{2+} handling are diverse and include ion channels and transporters on the plasma membrane and on organellar membranes. Here, we briefly review a few examples of Ca^{2+} channelopathies.

2.4.1. Plasma membrane Ca^{2+} channelopathies.

Ca^{2+} channels are expressed at the plasma membrane of almost all cell types and are involved in a plethora of cellular functions such as muscle contraction, neurotransmitter release, and fertilization. Different mechanisms govern Ca^{2+} channel activation, such as membrane potential changes (voltage-gated channels), ligand binding (ligand-gated channels), and Ca^{2+} depletion from intracellular stores (calcium release-activated channels).

Voltage-gated Ca^{2+} (Cav) channels are quite diverse from expression and function standpoints. Cav1.1 is specifically expressed in skeletal muscle, and therefore, all known Cav1.1 channelopathies are muscle diseases such as periodic paralysis, myopathies, malignant hyperthermia susceptibility, and myotonic dystrophy type 1. Cav1.4 is primarily expressed in the retina, explaining why Cav1.4 channelopathies lead to blindness. Mutations in the gene encoding Cav2.1 are linked to ataxia and migraine. A gain-of-function mutation in the gene encoding Cav1.2 causes Timothy syndrome, a multisystem disorder that affects the heart, the nervous system, and the digits (53). The syndrome is characterized by cardiac arrhythmias and fusion of digits (syndactyly).

Investigations have unraveled that defective Cav1.2 channel inactivation underlies the pathological enhancement of Ca^{2+} influx in cardiac myocytes (54), thus explaining the lethal arrhythmias.

The association of Timothy syndrome with syndactyly (54) pointed to a potential role for Cav channels in nonexcitable tissues. Recent work suggested that nonexcitable tissues expressing Cav1.2 are affected by the Timothy syndrome mutation leading to craniofacial development defects and immunodeficiency (55). We note that Cav1.2 function in nonexcitable cells is an interesting area that warrants further attention and has the potential to reveal novel aspects of voltage-gated channels (56). A recent study suggested, however, that pore-forming Cav subunits are truncated and nonfunctional in nonexcitable T cells, and further showed that auxiliary β-subunit regulates T-cell function independent of voltage-gated Ca^{2+} channel activity (57). It remains also unclear how Cav1.2 activation occurs in nonexcitable cells.

A crucial Ca^{2+} channel system in nonexcitable tissues is comprised of STIM1 (at the endoplasmic reticulum membrane) and ORAI1 (at the plasma membrane), which together form calcium release-activated channels. Loss-of-function mutations in genes encoding STIM1 and ORAI1 are linked to disorders such as muscular hypotonia, immunodeficiency, and ectodermal dysplasia. STIM1 and ORAI1 gain of function mutations cause tubular aggregate myopathy and Stormorken syndrome (58).

2.4.2. Organellar Ca^{2+} channelopathies.

While plasma membrane channelopathies are the primary focus of this article, equally important channels are expressed in organelles for which there are established channelopathies. Organellar Ca^{2+} handling mechanisms include channels that mediate Ca^{2+} release from the endoplasmic/sarcoplasmic reticulum (59). Ryanodine receptors (RyRs), for instance, mediate Ca^{2+} release into the cytosol and are prone to hundreds of mutations. Examples of RyR1 channelopathies in skeletal muscles are malignant hyperthermia, central core disease, and congenital myopathy. RyR2 mutations, on the other hand, are linked to cardiac diseases such as arrhythmias, catecholaminergic polymorphic ventricular tachycardia, and sudden cardiac death (59). Inositol 1,4,5-trisphosphate receptors (IP_3Rs) are also critically involved in Ca^{2+} release into the cytosol and IP_3R mutations cause diseases such as spinocerebellar ataxia, exocrine disorders, and cancer (59). Another organellar ion channel is the mucolipin transient receptor potential channel (TRPML1), which is Ca^{2+} permeable and predominantly expressed on the membranes of lysosomes. TRPML1 mutations lead to mucolipidosis IV and Niemann-Pick disease.

3. RECENT PHYSIOLOGICAL REVIEWS ARTICLES

Within the past few years, excellent reviews have been published in this journal and elsewhere on channelopathies, covering topics as broad as cancer, glomeruli function, and neuronal and muscle function.

No single ion channel gene mutation leads to uncontrolled proliferation, resistance to programmed cell death, tissue invasion, metastasis, and sustained angiogenesis. The recent *Physiological Reviews* article by Prevarskaya and colleagues (60), however, makes the case that abnormal ion channel activities (i.e., channelopathies) are involved in cancer and could even be regarded as "hallmarks" of the disease. Specific examples of ion channels involved in cancer include ORAI3, a Ca^{2+}-release activated Ca^{2+} channel in prostate cancer, and Nav1.5 in breast cancer. In the ORAI3 example, impaired Ca^{2+} signaling leads to increased proliferation and decreased apoptosis. In the Nav1.5 example, changes in membrane potential and the microenvironment lead to metastasis. The review further summarizes the contribution of many channels that affect cell proliferation and cell cycle progression in normal cells and during cancer. Because perturbations in so many transport proteins affect proliferation, migration, and apoptosis resistance, it is evident that cancer is a very complex disease involving the reconfiguration of entire biological processes. This reconfiguration also involves changes in endothelial cells and endothelial cell progenitors, therefore affecting new blood vessel formation. Several members of the transient receptor potential channel (TRPC) subfamily are implicated in stimulated angiogenesis (61). The review also underscores the murky line that separates ion channels from other membrane transport proteins, such as pumps, exchangers, and symporters disease (60). Many of these proteins are involved in the key processes affected by cancer: cell volume, proliferation, migration, and membrane potential. Irrespective of this distinction, the concept of onco-channelopathy is novel and worth further investigations.

The recent *Physiological Reviews* article on "Ion channels and channelopathies in glomeruli" (62) takes the reader through a systematic look at the different cell-types constituting this complex glomerular structure, their physiological roles in controlling glomerular filtration rate, and the many ion channels involved in the process of filtration (62). The human kidney consists of roughly 1 million nephrons, and each of these starts with a glomerulus or a filtering structure at the intersection between plasma and pro-urine. Among the cell types forming glomeruli are mesangial cells that fill the space between the vessels and possess contractile properties like those of smooth muscle cells. As such, mesangial

cells express ion channels involved in contractility: TRPCs and Cl^- channels, involved in depolarization; Cav channels, responding to depolarization and facilitating Ca^{2+} influx; large-conductance calcium-activated K^+ channels (BK_{Ca}); store-operated Ca^{2+} channels; purinergic receptors; and ATP-sensitive K^+ channels (K_{ATP}). Several channels of these are implicated in glomerular disease (63, 64). In distinction, podocytes are specialized "epithelial-like" cells sitting on top of the fenestrated endothelial cells. Podocytes allow water and solutes to pass through junctions, located at foot processes. Podocytes express a variety of ion channels, many of which are shared with mesangial cells. They also express TRPC5 and NMDA receptors, which are not found in mesangial cells. This is further complicated by the many intracellular (and extracellular in the case of ATP) factors that modulate ion channel function. A key channel involved in glomerular channelopathy is the nonselective calcium permeant cation channel TRPC6. Gain of function mutations in *TRPC6* lead to focal segmental glomerulosclerosis, a disease where 60% of affected individuals progress to end-stage renal disease. By discussing many aspects of TRPC6 biology (interaction with cytoskeleton, dysregulation by oxidative stress, effect of high glucose, etc.), the review proposes possible mechanisms for TRPC6 involvement in injury, loss, or dedifferentiation of podocytes. As complex as a "mini-organ" the glomerulus is with all its cell types and ion channels, it is not surprising that most ion channels mentioned above are involved in the etiology of glomerular disease.

The recent *Physiological Reviews* article by Mantegazza and colleagues (65) focused on monogenic sodium channelopathies of the brain and skeletal muscles. The opening of voltage-activated Na^+ channels is the first step in the creation of an action potential. This electrical signal drives contraction of skeletal and heart muscle cells and enables signal propagation along axons for neurons to communicate. The fourth transmembrane segment (S4) in the pore-forming alpha subunit of Nav1.x channels is sensitive to membrane voltage. In response to depolarization and hyperpolarization, the entire S4 segment moves up and down, thereby transmitting information to the pore. The pore is composed of the neighboring fifth and sixth transmembrane segments. The review by Mantegazza et al. (65) delves into the different regions of the Nav1.x protein that control the biophysical properties of the channel, and highlights the mutations in Nav1.4 (*SCN4A* gene) and Nav1.6 (*SCN8A* gene) leading to muscle paralysis (65). Mutations in segments coupling voltage sensor movement to pore opening in Nav1.4 cause hyperkalemic periodic paralysis. Mutations can also lead to paramyotonia congenita, potassium-aggravated myotonia, and other paralysis disorders. The list of Nav mutations is long, and different mutations in different domains will lead to diverse and complex clinical presentations. Importantly, mutations in Nav1.1 are linked to epilepsy, and therefore, the channels are targets for some antiepileptic drugs (e.g., phenytoin, carbamazepine). The severity of the epilepsy-causing mutation often determines the type of epilepsy experienced by the carrier. Nav1.1 is the most frequently mutated Na^+ channel leading to a spectrum of epilepsy syndromes ranging from mild febrile seizures to intractable, drug-resistant developmental and epileptic encephalopathies (66).

4. CONCLUDING REMARKS

Hundreds of human genes encode for ion channels. Considering the intimate involvement of ion channels in almost all aspects of physiology, it is well established that ion channel modulation or dysfunction is linked to a variety of diseases such as arrhythmias, cystic fibrosis, and epilepsy. The first use of the term "channelopathy" dates to three decades ago. Discoveries unraveling channelopathies and their impacts on human health continue to expand. This is, in part, attributed to recent advances in our understanding of the role of ion channels in human physiology and pathophysiology and high-throughput genetic screens of large human populations.

Similar to G protein-coupled receptors, which are the most studied drug targets, ion channels are well recognized as important therapeutic targets for treating several diseases (e.g., calcium channels blockers as antihypertensive medications; sodium channel blockers as antiepileptic drugs). Understanding channelopathies, whether genetic or acquired and whether attributed to changes in ion channels themselves or in interacting proteins or lipids (**FIGURE 1**), holds a significant potential for the development of therapeutic interventions that are most needed.

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AUTHOR CONTRIBUTIONS

O.F.H. and E.D. prepared figures; O.F.H. and E.D. drafted manuscript; O.F.H. and E.D. edited and revised manuscript; O.F.H. and E.D. approved final version of manuscript.

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