Symposium

More Than a Pore: Ion Channel Signaling Complexes

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Voltage- and ligand-gated ion channels form the molecular basis of cellular excitability. With >400 members and accounting for ~1.5% of the human genome, ion channels are some of the most well studied of all proteins in heterologous expression systems. Yet, ion channels often exhibit unexpected properties *in vivo* because of their interaction with a variety of signaling/scaffolding proteins. Such interactions can influence the function and localization of ion channels, as well as their coupling to intracellular second messengers and pathways, thus increasing the signaling potential of these ion channels in neurons. Moreover, functions have been ascribed to ion channels that are largely independent of their ion-conducting roles. Molecular and functional dissection of the ion channel proteome/interactome has yielded new insights into the composition of ion channel complexes and how their dysregulation leads to human disease.

Introduction

Ion channels are multimeric assemblies consisting of a central ion-conducting pore and a variable number of additional proteins. These channel-interacting proteins (CIPs) may act as obligate subunits in that their only known function is to regulate channel parameters, such as gating, permeation, and/or trafficking to the cell surface or particular subcellular microdomains. Voltage-gated Na^+, K^+, and Ca^{2+} channels each associate with one or more non–pore-forming subunits that are structurally and functionally distinct (Li et al., 2006; Buraei and Yang, 2010; Dolphin, 2013; Calhoun and Isom, 2014; Jerng and Pfaffinger, 2014). Other CIPs are common signaling or scaffolding proteins that can influence the function of ion channels and/or their coupling to downstream pathways. For example, A-kinase anchoring protein (AKAP) tethers cAMP-dependent protein kinase and calcineurin, which can regulate the phosphorylation status, and modulation, of the Ca_v1 L-type Ca^{2+} channel (Dittmer et al., 2014; Fuller et al., 2014) and the K_v7 M-type K^+ channel (Zhang et al., 2011), as well as the role of Ca_v1 channels in transcriptional signaling (Zhang and Shapiro, 2012; Murphy et al., 2014). G-protein-coupled receptors represent another class of CIPs that associate with a variety of ion channels, including N-methyl-D-aspartate receptor (NMDAR) glutamate-gated channels. NMDARs associate with D_1 and D_2 dopamine receptors, which mediate inhibition of NMDAR function in response to D_1 and D_2 receptor agonists (Lee et al., 2002; Liu et al., 2006).

Genetic variations that disrupt the association of ion channels with CIPs cause a variety of human disorders, such as Liddle syndrome, cardiac arrhythmia, diabetes mellitus, and epilepsy (Jackson and Nicoll, 2011; Kline and Mohler, 2014; Bao and Isom, 2014 ; O'Malley and Isom, 2014). Moreover, drugs that stabilize CIP/channel interactions are being developed as novel therapeutic strategies (Andersson and Marks, 2010). Therefore, the characterization of the ion channel proteome/interactome has been the subject of intense investigation, requiring an interdisciplinary battery of proteomics, biochemistry, and electrophysiology, combined with the development of new animal models. These studies have greatly expanded our view of ion channels as macromolecular signaling complexes, the constituents of which define the properties and function of these channels in a cell-type-specific manner. Given the wealth of knowledge that has emerged on ion channel-signaling complexes, this review is not meant to be comprehensive but highlights some recent advances in our understanding of CIP/ion channel interactions in the context of neuronal signaling.

Analyzing native ion channels by "functional proteomics"

The comprehensive analysis of ion channels and CIPs in their native cellular environment represents a major challenge. Such analysis ideally requires the intact isolation of the "native" ion channels and the unbiased identification of their constituents. Technical limitations have hampered such strategies, leaving more indirect approaches based on molecular biology (such as expression or siRNA-based cloning and yeast-two-hybrid arrest) or on genetic analysis of distinct (disease-related) phenotypes. However, recent advances in protein biochemistry and, in particular, high-resolution mass spectrometry, have enabled direct access to native ion channels in their microenvironments through unbiased proteomics technologies (for review, see Schulte et al., 2011).

The respective workflow, termed "functional proteomics" (Müller et al., 2010), comprises several distinct experimental steps:

(1) Initially, appropriately solubilized membrane fractions are set up that are prepared from the tissue expressing the channel of interest and finally come as a suspension of inhomogeneous membrane-surrounded vesicles/fragments (Mena et al., 1980). Prepared from brain, these protein fractions are often called "synaptosomal fractions" as they show some enrichment of presynaptic and postsynaptic membranes/proteins, but, important to note, also contain membranes/proteins from cell bodies and dendrites, as well as from the various intracellular membrane compartments (Müller et al., 2010). Solubilization requires careful selection of detergents as they may, in addition to acting as a solvent, destabilize protein–protein interactions and thus perturb the integrity of protein complexes. Consequently, the preservation of higher molecular weight assemblies of the target protein must be assessed, most directly by native gel electrophoresis (Berkefeld et al., 2006; Schwenk et al., 2012).

(2) The channel protein(s) are then extracted from these solubilized membrane fractions by affinity matrices consisting of immobilized antibodies targeting the ion channel of interest, either via the pore-forming α-subunit or tightly associated auxiliary subunits. This step benefits from the use of multiple antibodies recognizing different epitopes because single antibodies may exhibit cross-reactivity to other proteins or may extrude interacting proteins from the target (Schulte et al., 2011). Alternatively, the ion channel complexes may be isolated by native gel electrophoresis and excision of the target-containing gel sections (Schwenk et al., 2012).

(3) The isolated/enriched protein samples are then analyzed by high-resolution nano-flow mass spectrometry (LC-MS/MS). This approach provides unbiased information on both the amount (intensity of precursor ions in the MS spectra) and identity of any protein in the sample (via fragmentation resulting in MS/MS spectra resulting from fragmentation). The protein amounts can be quantified by various methods (Beynon et al., 2005; Ong and Mann, 2006; Cox and Mann, 2008; Nanavati et al., 2008; Bildl et al., 2012), of which label-free quantification of MS signals from precursor peptides is favored because of its extended dynamic range of up to as much as four orders of magnitude (Bildl et al., 2012).

(4) Finally, the protein amounts are used to discriminate the proteins that are specifically copurified with the target (ion channel) from background. For this purpose, protein amounts in affinity purifications with the target-specific antibodies are first related to two types of negative controls: affinity purifications with preimmunization immunoglobulins (IgGs) and affinity purifications with the target-specific antibodies from membrane fractions of target knock-out animals. Subsequently, all proteins dubbed specific for any individual target-specific antibody are probed for consistent appearance across all target-specific antibodies to discard all the single "hits" resulting from the particular properties of individual target antibodies. With these criteria of specificity and consistency, one can identify the entire set of proteins that reconstitute a given ion channel in native membranes,

termed "proteome" (or sometimes "interactome") of that particular channel (Müller et al., 2010; Schwenk et al., 2012).

This workflow has been successfully applied to various types of ion channels (Nadal et al., 2003; Berkefeld et al., 2006; Schulte et al., 2006; Marionneau et al., 2009; Schwenk et al., 2009; Zolles et al., 2009; Müller et al., 2010; Schwenk et al., 2012). Of these, glutamate receptors of the AMPA-type (AMPARs) represent an ideal example to demonstrate the benefit of unbiased proteomic analysis for studying architecture and function of ion channels in the context of native cells and/or tissue.

Based on molecular cloning and phenotype analysis, AMPARs were assumed to consist of four GluA proteins and a family of transmembrane AMPAR regulatory proteins (TARPs) (Tomita et al., 2003; Milstein et al., 2007). However, comprehensive proteomic analysis with 10 different antibodies against the four pore-forming GluA proteins identified AMPARs in the rodent brain as macromolecular complexes assembled from a pool of >30 different proteins, mostly transmembrane proteins of different classes and secreted proteins (Schwenk et al., 2012). These findings revealed unanticipated molecular diversity for native AMPARs but also defined some principles behind their assembly. AMPARs exhibit a "layered" architecture, consisting of a defined core and a more variable periphery (Schwenk et al., 2012). The receptor core is formed by tetramers of the pore-forming GluA1–4 proteins (Seeburg, 1993; Hollmann and Heinemann, 1994) and up to four members of three distinct families of membrane proteins that serve as classical auxiliary subunits: TARPs (TARPs, γ-2, γ-3, γ-4, γ-5, γ-7, γ-8), the cornichon homologs 2 and 3 (CNIH2, 3) (Schwenk et al., 2009), and the GSG1-l protein (Fig. 1A) (Schwenk et al., 2012; Shanks et al., 2012). The periphery of the receptors is built from a set of transmembrane and/or soluble proteins that include CKAMPs 44, 52 (von Engelhardt et al., 2010), CPT-1, C9orf 4, Brorin2, Noelins1–3, Neuritin, PRRTs 1,2, and LRRT4 (Siddiqui et al., 2013), as well as four isoforms of the MAGUK family (Schwenk et al., 2012) (Fig. 1A,B).

The assembly of different proteins within this combinatorial architecture can greatly influence AMPAR function. The inner core largely determines the biophysical properties of the receptor channels, which includes agonist-triggered gating, ion selectivity and permeation, or block by polyamines, and influences their biogenesis, protein processing, and/or trafficking (Chen et al., 2000; Tomita et al., 2005; Bats et al., 2007; Cho et al., 2007; Soto et al., 2007; Schwenk et al., 2009; Soto et al., 2009; Kato et al., 2010; Coombs et al., 2012; Studniarczyk et al., 2013). In heterologous expression experiments, TARPs, CNIHs, and GSG1l (Fig. 1A) impact the gating of the AMPARs, either alone or in combination, by distinctly slowing deactivation and desensitization of various GluA homo-tetramers or hetero-tetramers (Schwenk et al., 2009, 2012). Among those auxiliary subunits, the two CNIH proteins exert the strongest influence, slowing the time constants of either channel-closing process by up to more than fivefold, independent of the GluA composition of the pore (Schwenk et al., 2009; Kato et al., 2010; Coombs et al., 2012). The neurophysiological significance of CNIH2 in prolonging AMPAR currents was demonstrated by the acceleration in the decay of EPSCs upon virus-directed knock-down of CNIH2 in hippocampal mossy cells and, vice versa, by the pronounced slowing of the postsynaptic currents in the neighboring interneurons upon virus-mediated expression of CNIH2 (Boudkkazi et al., 2014). The proteins comprising the periphery of AMPAR influence various aspects of AMPAR function (von Engelhardt et al., 2010) or traf-
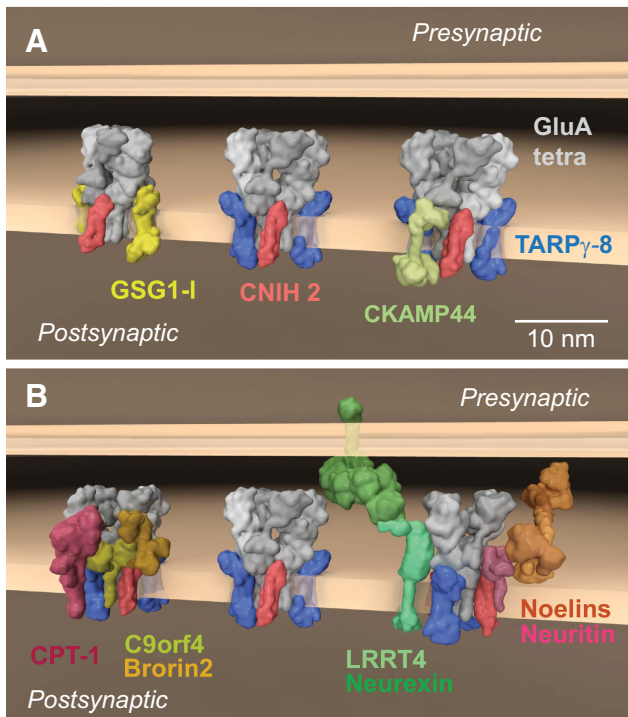
Figure 1. Molecular diversity of AMPAR assemblies. **A**, **B**, Different macromolecular AMPAR assemblies of distinct subunit composition as identified by functional proteomics in the whole rodent brain (Schwenk et al., 2009, 2012). All proteins are presented as space-filling 3D models that are projected onto the postsynaptic membrane. The models were generated with the Maya platform (Autodesk Maya 3D) (Takamori et al., 2006) using pdb-entries and molecular modeling for the indicated proteins.

ficking (Cantallops et al., 2000; Chen et al., 2000; Zhu et al., 2002; Hussain et al., 2010; Siddiqui et al., 2013). It must be emphasized, however, that many of the physiological implications of the periphery-forming AMPAR constituents are not clear because they currently lack defined primary functions.

Nevertheless, the characterization of the AMPAR proteome will undoubtedly motivate investigations into the function of these proteins and guide future analyses of the molecular mechanisms underlying the observed functional diversity of AMPARs.

CaBPs enhance the functional diversity and cellular regulation of voltage-gated Ca_v1 Ca^{2+} channels

Quantitative proteomic analyses have revealed that voltage-gated Ca^{2+} channels, like AMPARs, are embedded in complex protein nano-environments (Müller et al., 2010). Ca_v channels consist of a main pore-forming α_1 subunit and an auxiliary $Ca_v\beta$ and $\alpha_2\delta$ subunit (Fig. 2A), which alter channel activation, inactivation, and/or cell-surface trafficking (Buraei and Yang, 2010; Dolphin, 2013; Simms and Zamponi, 2014). Of the multiple classes of Ca_v channels that have been characterized, Ca_v1 Ca^{2+} channels mediate L-type Ca^{2+} currents in nerve and muscle. $Ca_v1.2$ and $Ca_v1.3$ are the most highly expressed Ca_v1 channels in the brain (Schlick et al., 2010), where they regulate neuronal excitability (Marrion and Tavalin, 1998; Puopolo et al., 2007), activity-dependent gene transcription (Ma et al., 2013), and synaptic plasticity (Moosmang et al., 2005). $Ca_v1.4$ and $Ca_v1.3$ are the primary Ca_v1 channels in retinal photoreceptors and cochlear inner hair cells, respectively (Platzer et al., 2000; Brandt et al., 2003; Mansergh et al., 2005).

Ca_v1 channels interact with a variety of CIPs (Calin-Jageman and Lee, 2008; Dai et al., 2009), including the EF-hand Ca^{2+}
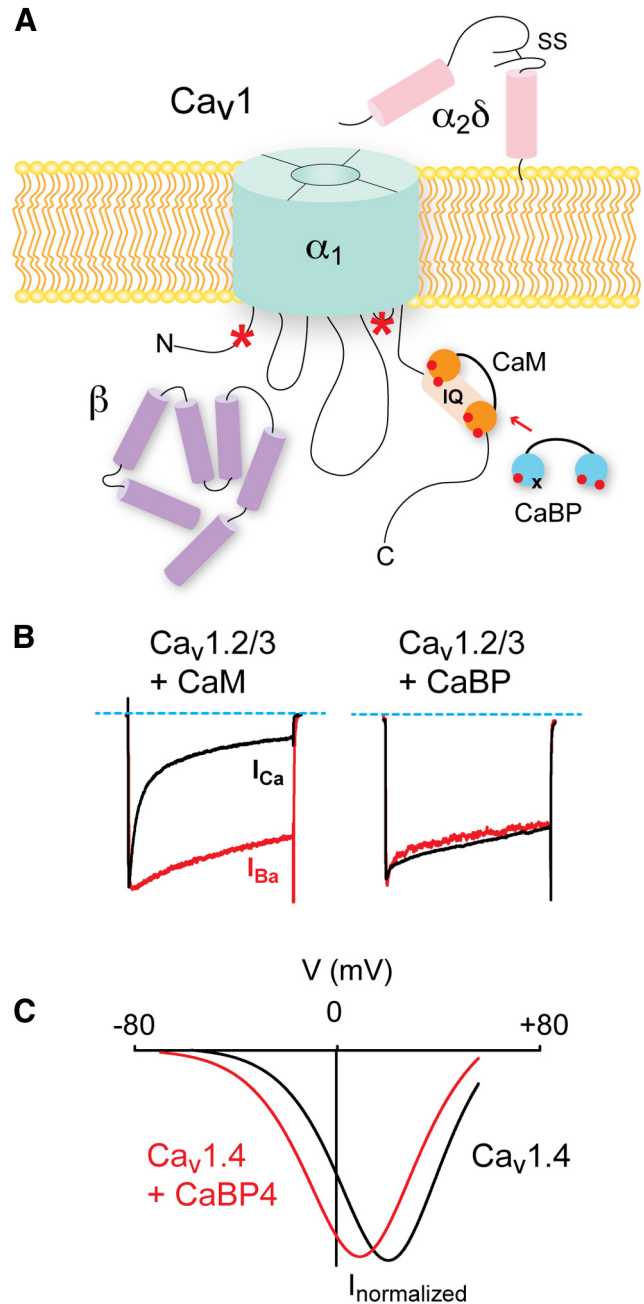
Figure 2. Distinct modulation of Ca_v1 channels by CaM and CaBPs. **A**, Ca_v complexes consist minimally of α_1, β, and $\alpha_2\delta$ subunits. CaM and CaBPs bind to the IQ domain, but other CaBP binding sites exist in the N-terminal domain and III-IV linker (*). **B**, For $Ca_v1.2$ and $Ca_v1.3$ channels, CDI due to CaM manifests as faster inactivation of Ca^{2+} (I_{Ca}) currents compared with Ba^{2+} currents (left). CaBPs prevent CDI (right). Modified from Zhou et al. (2004). **C**, Current–voltage relation demonstrating effect of CaBP4 in potentiation of $Ca_v1.4$ channels by causing a negative shift in voltage-dependent activation (red trace). Modified from Haeseleer et al. (2004).

sensor, calmodulin (CaM). Tethered to a consensus IQ domain in the C-terminal domain of the Ca_v1 α_1 subunit (Fig. 2A), CaM binds incoming Ca^{2+} ions and initiates conformational changes in the channel protein that underlie Ca^{2+}-dependent inactivation (CDI) (Fig. 2B) (Peterson et al., 1999; Qin et al., 1999; Zühlke et al., 1999; for review, see Ben-Johny and Yue, 2014). In the heart, Ca^{2+}/CaM-driven CDI accelerates the decay of $Ca_v1.2$ channel Ca^{2+} currents, which prevents excessively long cardiac action potentials that can cause arrhythmia (Alseikhan et al.,

2002). CDI has also been described for Ca_v channels in neurons (Budde et al., 2002) and may be neuroprotective in preventing excitotoxic Ca^{2+} overloads (Nägerl et al., 2000). Multiple factors can influence the extent to which Ca_v1 channels undergo CDI (Christel and Lee, 2012). In hippocampal neurons, AKAP anchoring of cAMP-dependent protein kinase promotes phosphorylation and potentiation of Ca_v1 channels. This in turn primes channels to undergo CDI, here due to dephosphorylation by calcineurin associated with the AKAP/Ca_v1 channel complex (Dittmer et al., 2014).

Other CIPs that play important CDI-modulatory roles are a family of CaM-like Ca^{2+} binding proteins (CaBPs) that are highly expressed in the brain, retina, and inner ear (Seidenbecher et al., 1998; Haeseleer et al., 2000, 2004; Yang et al., 2006; Cui et al., 2007; Kim et al., 2014). Like CaM, CaBPs have 4 EF-hand Ca^{2+} binding domains, at least one of which is nonfunctional (Haeseleer et al., 2000). In heterologous expression systems, CaBPs inhibit CDI of $Ca_v1.2$ and $Ca_v1.3$ (Zhou et al., 2004; Yang et al., 2006; Cui et al., 2007; Tippens and Lee, 2007) (Fig. 2B). The mechanism likely involves displacement of CaM from the Ca_v1 α_1 IQ domain (Zhou et al., 2004; Findeisen et al., 2013; Oz et al., 2013) (Fig. 2A). However, CaBPs can bind to multiple sites in Ca_v1 α_1, and so, may allosterically modulate CaM interactions with the channel (Zhou et al., 2005; Oz et al., 2011; Yang et al., 2014).

The distinct tissue distribution of CaBP family members suggests that they may regulate different Ca_v1 channels (Haeseleer et al., 2000, 2004). Alternative splicing produces 3 CaBP1 variants (CaBP1-S, CaBP1-L, and caldendrin), which associate with $Ca_v1.2$ channels in the brain (Zhou et al., 2004; Tippens and Lee, 2007). When coexpressed with $Ca_v1.2$ in heterologous systems, both CaBP1 and caldendrin strongly suppress CDI, but through slightly different molecular determinants. Although mutations of the IQ domain strongly diminish the impact of both caldendrin and CaBP1, CaBP1 but not caldendrin binds to the N-terminal domain of $Ca_v1.2$ α_1, and deletion of this N-terminal site inhibits modulation by CaBP1 but not caldendrin (Zhou et al., 2004; Tippens and Lee, 2007). Caldendrin is expressed at higher levels than either CaBP1 variant and, in the frontal cortex, undergoes a developmental increase in expression that parallels the time course of cortical synaptogenesis (Laube et al., 2002; Kim et al., 2014). Caldendrin may be important for prolonging Ca_v1 Ca^{2+} signals that promote the formation of dendritic arbors during development (Redmond et al., 2002), although caldendrin also regulates synapse number via NMDA receptor signaling (Dieterich et al., 2008).

In the cochlea, antibodies against CaBP1, CaBP2, CaBP4, and CaBP5 strongly label inner hair cells (Yang et al., 2006; Cui et al., 2007). In transfected HEK293T cells, all four CaBPs inhibit CDI of $Ca_v1.3$ channels (Yang et al., 2006; Cui et al., 2007; Schrauwen et al., 2012). Unlike the transient $Ca_v1.3$ Ca^{2+} currents due to CaM-driven CDI, the sustained $Ca_v1.3$ Ca^{2+} currents caused by CaBPs would support tonic glutamate release necessary for sound coding at the inner hair cell ribbon synapse. A mutation that impairs CaBP2 modulation of $Ca_v1.3$ CDI causes autosomal recessive hearing loss in humans (Schrauwen et al., 2012), although the phenotype is not as severe as the profound deafness seen in patients with a loss-of function mutation in the *CACNA1D* gene encoding $Ca_v1.3$ α_1 (Baig et al., 2011). The presence of other CaBPs may compensate for a deficit in CaBP2 modulation. However, other mechanisms may jointly suppress CDI of $Ca_v1.3$ in inner hair cells, such as alternative splicing of $Ca_v1.3$

α_1 transcripts (Shen et al., 2006) or interactions with other inner hair cell proteins (Gebhart et al., 2010).

In the retina, CaBP4 is highly localized in photoreceptor terminals, where it interacts with the IQ domain of the $Ca_v1.4$ α_1 subunit (Haeseleer et al., 2004). Unlike $Ca_v1.2$ and $Ca_v1.3$, $Ca_v1.4$ channels undergo little CDI even in the absence of CaBPs. CaM can still bind to the $Ca_v1.4$ α_1 IQ domain, but this interaction is disrupted by an autoregulatory C-terminal domain (ICDI: inhibitor of CDI). Deletion of the ICDI permits CaM-dependent CDI (Singh et al., 2006; Wahl-Schott et al., 2006), which is then blunted by CaBP4 (Shaltiel et al., 2012). The similar effects of CaBP4 and the ICDI in suppressing CDI are likely due to each competing for occupancy of the IQ domain (Shaltiel et al., 2012). However, a second, and likely the major, effect of CaBP4 is to shift the voltage dependence of activation to more negative voltages (Haeseleer et al., 2004; Shaltiel et al., 2012) (Fig. 2C). This effect of CaBP4 is prevented by deletion of the ICDI (Shaltiel et al., 2012), suggesting that interactions between the ICDI, CaBP4, and the IQ domain are required for modulation of channel gating by CaBP4. Association of $Ca_v1.4$ channels with CaBP4 would promote Ca^{2+} influx at the relatively depolarized membrane potential of photoreceptors in darkness (~-40 mV). This in turn may enhance the gain of rod photoreceptor synapses by ensuring sufficient activation of postsynaptic metabotropic glutamate receptors and subsequent hyperpolarization of ON rod bipolar cells in darkness. Mice lacking CaBP4 exhibit impaired rod bipolar responses to light stimuli, consistent with loss of function of $Ca_v1.4$ (Haeseleer et al., 2004). Moreover, mutations in the *CaBP4* gene, which disrupt CaBP4 modulation of $Ca_v1.4$, cause vision impairment in humans (Zeitz et al., 2006; Littink et al., 2009; Shaltiel et al., 2012). Together, these studies illustrate the importance of CaBPs as CIPs that can facilitate Ca_v1 Ca^{2+} influx in various neuronal cell types.

Na_v β subunits are multifunctional regulators of neuronal excitability and cell adhesion

Voltage-gated Na_v Na^+ channels generate the rising phase and propagation of the action potential in excitable cells, including neurons and cardiac myocytes. Like Ca_v channels, Na_v channels are comprised of one pore-forming α subunit (Fig. 3A). The Na_v α subunit can associate with one or more β subunits, which are structurally distinct from Ca_v β subunits (Fig. 3A). Originally characterized as "auxiliary" subunits that solely regulate Na_v channel function, Na_v β subunits are now known to play essential and diverse roles in a variety of cell types with or without Na_v α subunits. The physiological importance of Na_v β subunits is illustrated by the numerous and severe disorders linked to mutations in the encoding genes. These include epilepsy (e.g., Dravet Syndrome with sudden unexpected death in epilepsy), cardiac arrhythmia, and sudden infant death syndrome. In addition, changes in Na_v β subunit expression are thought to modulate pain, demyelinating and neurodegenerative disorders, cancer, and autism spectrum and mood disorders (O'Malley and Isom, 2014). Five Na_v β subunit proteins are encoded by a family of four genes, denoted *SCNXB*: $\beta1$ and its splice variant $\beta1B$ (*SCN1B*); $\beta2$, $\beta3$, and $\beta4$ (*SCN2B*, *SCN3B*, and *SCN4B*, respectively) (O'Malley and Isom, 2014).

In heterologous expression systems, $\beta1$ can negatively shift the voltage dependence of Na_v channel activation and inactivation, and speed inactivation kinetics (Isom et al., 1992). Although these actions of $\beta1$ on Na_v properties are subtle *in vivo*, genetic inactivation of *SCN1B* severely impairs cellular excitability in the brain and heart (Chen et al., 2004; Lopez-Santiago et al., 2007;

A

B
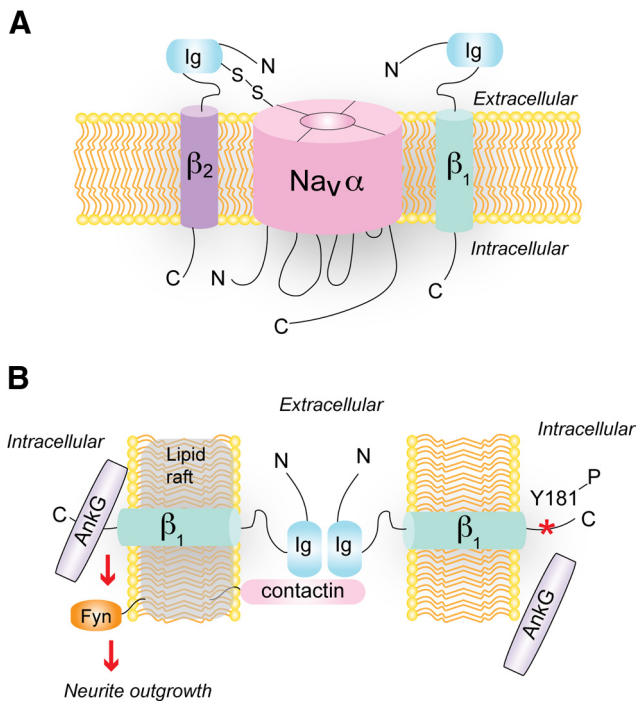
Figure 3. Auxiliary and nonauxiliary roles of Na$_v$β subunits. **A**, One or more β subunits interact with and regulate Na$_v$ α subunits. β$_2$ (and β$_4$) are covalently linked, whereas β$_1$ (and β$_3$) are noncovalently linked, to the α subunit. **B**, Role of Na$_v$β$_1$ in cell adhesion. β$_1$ is localized in lipid rafts with contactin and forms trans-homophilic interactions with other β$_1$ subunits. This is postulated to activate fyn kinase signaling and neurite outgrowth. AnkyrinG (AnkG) is recruited to sites of cell–cell contact through interactions with the C-terminal domain of β$_1$. When a specific tyrosine residue in the β$_1$ C terminus is (Y181, *) phosphorylated (presumably by fyn kinase), AnkG association is inhibited.

Brackenbury et al., 2013). Paradoxically, dorsal root ganglion and cortical neurons from *SCN1B* null mice are hyperexcitable (Lopez-Santiago et al., 2007; Marionneau et al., 2012; Brackenbury et al., 2013), which may be due to effects of β1 on K$_v$ channels. β1 interacts directly with K$_v$4.2 A-type K$^+$ channels and increases the cell-surface density of these channels. In layer V cortical pyramidal cells from *SCN1B* null mice, A-type K$^+$ current density is reduced and repetitive firing is increased (Marionneau et al., 2012). β1 also interacts with K$_v$4.3 channels in the heart and increases K$_v$4.3 current density both in cardiac myocytes and transfected HEK293 cells (Deschênes and Tomaselli, 2002; Deschênes et al., 2008). By partnering with either Na$_v$ or K$_v$ channels, Na$_v$ β subunits can powerfully modulate cellular excitability.

In addition to their role in modulating ion channel function, Na$_v$ β subunits act as cell adhesion molecules (CAMs). All five β subunits contain an extracellular immunoglobulin (Ig; Fig. 3A) domain homologous to V-type Ig loop motifs present in the Ig superfamily of CAMs (Isom, 2001). Like other CAMs of the Ig superfamily, β subunits can interact with each other trans-homophilically to induce signaling in adjacent cells (Fig. 3B). In *Drosophila* S2 cells, exogenously expressed β1 or β2 leads to aggregation of cells and recruitment of ankyrinG at sites of cell–cell contact. AnkyrinG interacts with β subunits and recruitment of ankyrinG to cell–cell contacts, but not cell aggregation, is prevented by deletion of the cytoplasmic C-terminal domain of either β subunit and by phosphorylation of tyrosine (Y)181 in this region (Malhotra et al., 2000, 2002) (Fig. 3B). In the heart, phosphorylation of Y181 prevents the interaction of β1 with

ankyrin but promotes the interaction of β1 with N-cadherin. Moreover, β1 subunits with phosphorylated Y181 colocalize with N-cadherin at intercalated disks, but not with ankyrin at *t*-tubules (Malhotra et al., 2004). The intracellular domain of β1 interacts with receptor tyrosine phosphatase β, which regulates the modulatory impact of β1 on Na$_v$ channels in transfected tsA-201 cells (Ratcliffe et al., 2000). By opposing phosphorylation of Y181, receptor tyrosine phosphatase β could enhance interactions of β1 with ankyrin, which may dynamically regulate the subcellular localization of Na$_v$ channels.

In neurons, the association of Na$_v$ β subunits with distinct subsets of proteins determines their subcellular localization and function. At the axon initial segment, Na$_v$ β4 is recruited by Na$_v$ α subunits through a disulfide linkage formed between Na$_v$ α and an extracellular cysteine in β4 (Buffington and Rasband, 2013). Na$_v$ β4 mediates resurgent Na$^+$ current, a transient increase in Na$^+$ conductance upon membrane repolarization (Raman and Bean, 1997; Grieco et al., 2005). Because the activity of Na$_v$ channels in the axon initial segment regulates action potential generation (Khaliq and Raman, 2006), the targeting of Na$_v$ β4 to the axon initial segment should strongly influence neuronal excitability. Consistent with this prediction, siRNA knockdown of *SCN4B* depresses repetitive firing in cerebellar granule neurons (Bant and Raman, 2010). At nodes of Ranvier, β subunits colocalize with Na$_v$ α subunits and are thus positioned to modulate channels during rapid saltatory conduction of action potentials (Chen et al., 2002, 2004). In the paranodal subcompartment adjacent to the nodal gap, β1 interacts with a trimeric complex of axo-glial paranodal proteins consisting of contactin, Caspr, and glial neurofascin-155 (Kazarinova-Noyes et al., 2001; McEwen et al., 2004). The localization of β1 to this subcellular compartment may contribute to the establishment and maintenance of paranodes and formation of the nodal gap: paranodal structure is abnormal in *SCN1B* null mice, which may contribute to the ataxia observed in these animals (Chen et al., 2004).

In addition to ataxia, *SCN1B* null mice undergo spontaneous seizures beginning around postnatal day (P)10 (Chen et al., 2004). Before the development of hyperexcitability at P5, *SCN1B* null mice exhibit defects in neuronal proliferation, migration, and pathfinding (Brackenbury et al., 2013). In cerebellar granule neurons, Na$_v$ β1 promotes neurite outgrowth through trans-homophilic interactions (Davis et al., 2004), and this effect requires contactin and the lipid raft-associated tyrosine kinase fyn (Brackenbury et al., 2008) (Fig. 3B). Interestingly, Na$_v$ β subunits have been detected in lipid rafts, where they are substrates for sequential cleavage by β- (BACE) and γ-secretases implicated in the pathology of Alzheimer's disease (Wong et al., 2005). These results highlight a key role for Na$_v$ β subunits as CAMs required for normal development of neural circuits, as well as multifunctional regulators of ion channels and neuronal excitability in the mature nervous system.

Interactions of K$^+$ channels with cytoplasmic signaling pathways

Within the ion channel superfamily, K$^+$ channels are the most diverse at the molecular level, with >80 genes encoding K$^+$ channel α subunits. In contrast to the single polypeptide forming the pore of Na$_v$ and Ca$_v$ channels, functional K$^+$ channels are comprised of homomers or heteromers of four α subunits (Fig. 4A; two in the case of the K$_{2P}$ subfamily). This diversity is unlikely to represent functional redundancy and suggests that different members of the K$^+$ channel family have roles that go beyond simply regulating K$^+$ flux across the plasma membrane.

A variety of studies have shown that K$^+$ channels interact directly with cytoplasmic and cytoskeletal proteins and that the gating of channels can trigger cytoplasmic signaling even when ion flux through the pore of the channel has been eliminated (Kaczmarek, 2006). Some subfamilies of voltage-gated K$_v$ K$^+$ channels have their own classes of auxiliary subunits (Li et al., 2006). These subunits are not required for ion permeation but regulate trafficking and gating and may be required for modulation of the channels by protein kinases or other signaling pathways (Vacher and Trimmer, 2011). For example, the pore-forming α-subunits of K$_v$1 channels interact with one of three K$_v$ β subunits. Two of these are functional aldo-keto reductases that use NADPH as a cofactor. Activation of these attached enzymes directly regulates inactivation and amplitude of K$_v$1 currents. Moreover, direct phosphorylation of the K$_v$ β subunits is required for appropriate trafficking and targeting of these channels to axons (Vacher and Trimmer, 2011).

In some cases, K$_v$ channel auxiliary subunits mediate interactions with other ion channels. For example, Ca^{2+}-activated BK K$^+$ channels form complexes with Ca$_v$ Ca^{2+} channels (Berkefeld et al., 2006). Ca$_v$ channels can also interact with K$_v$ channels via the K$_v$ auxiliary subunits. KChiPs are members of a family of neuronal Ca^{2+}-binding proteins that interact with K$_v$4 channels and regulate their voltage dependence of inactivation (Li et al., 2006; Vacher and Trimmer, 2011). In some neurons, KChiPs exist in ternary complex with K$_v$4.2 K$^+$ channels and Ca$_v$3 T-type Ca^{2+} channels (Anderson et al., 2010). These K$_v$/Ca$_v$ channel complexes would allow for precise timing of neuronal hyperpolarization following depolarization, due to very local regulation of K$_v$ channels by Ca^{2+} that enters through the pore of the Ca$_v$ channel.

Na$^+$-activated K$^+$ channels represent an additional class of K$^+$ channels that shape the excitability of neurons in the CNS and are encoded by the *Slack* and *Slick* genes (also termed *Slo2.2* and *Slo2.1*, or *KCNT1* and *KCNT2*, respectively) (Joiner et al., 1998; Yuan et al., 2003; Bhattacharjee et al., 2005). The fact that the C-terminal cytoplasmic domains of these channels are particularly large prompted a search for cytoplasmic proteins that may interact with these domains. At least one such interacting protein is the Fragile X Mental Retardation Protein (FMRP; Fig. 4A) (Brown et al., 2010; Zhang et al., 2012).

FMRP is an RNA-binding protein that is required for some forms of activity-dependent protein translation within neurons and may be particularly important for local translation in den-
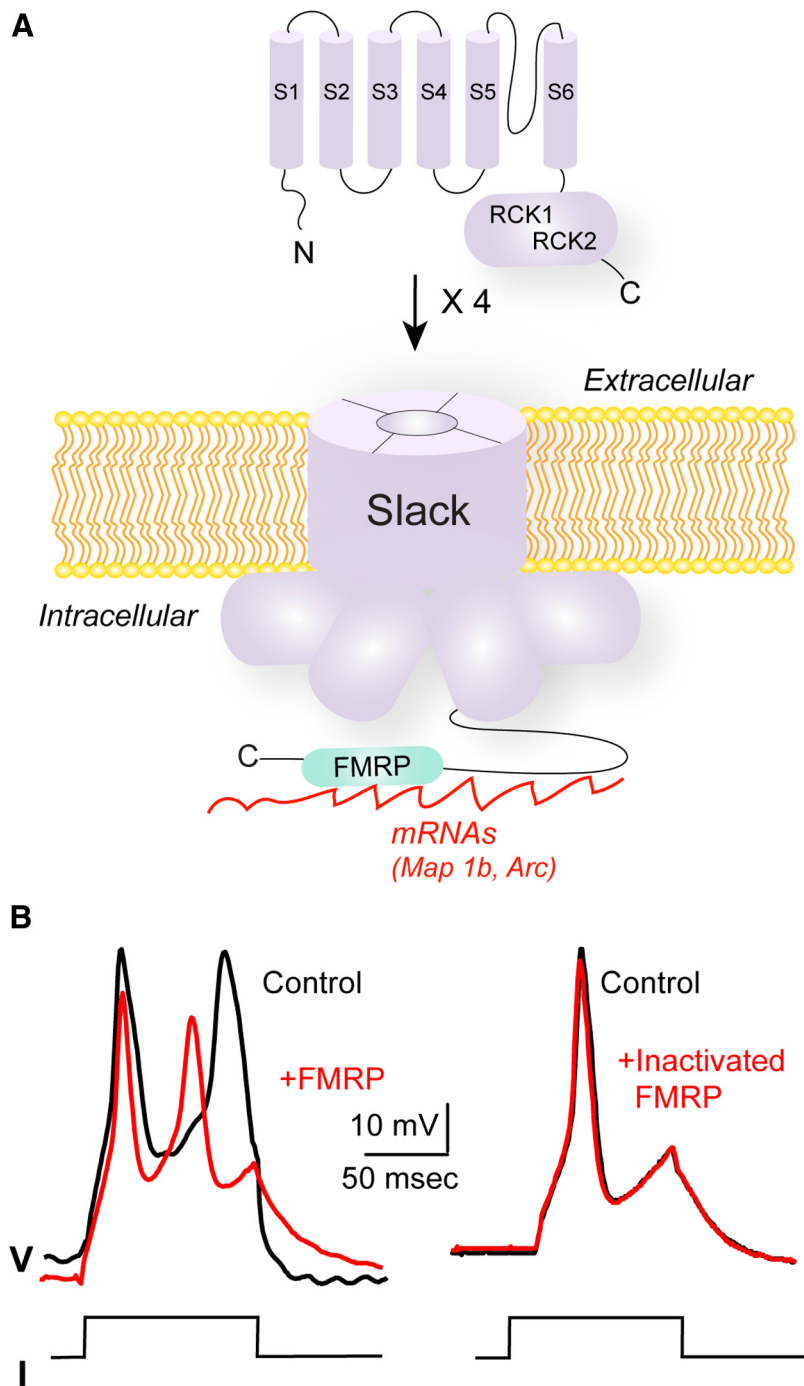
Figure 4. Interaction of the Slack Na$^+$-activated K$^+$ channel with FMRP. **A**, Slack subunits have six transmembrane domains (S1–S6); four of these subunits form the channel. The bulk of the channel protein resides in the cytoplasmic C-terminal domain of each subunit (solid and dashed lines), which contains two regulator of K$^+$ conductance domains (RCK1, RCK2). FMRP and its target RNAs interact with the C-terminal domain of Slack. **B**, Injection of FMRP(1–298) hyperpolarizes membrane potential in *Aplysia* neurons. Representative traces of the effect of injection of FMRP(1–298) or heat-inactivated FMRP(1–298) on action potentials of *Aplysia* bag cell neurons. Action potentials were evoked by injecting 0.6 nA current pulses. Modified from Zhang et al. (2012).

drites or compartments other than the soma (Bassell and Warren, 2008). Loss of FMRP results in Fragile X syndrome, the most common inherited form of intellectual disability in humans. This condition is also associated with hypersensitivity to sensory stimuli, particularly auditory stimuli, and with an increased incidence of epilepsy during childhood (10%–18%). Interactions between FMRP and the cytoplasmic C-terminal domain of Slack have been demonstrated by yeast two-hybrid and coimmunoprecipi-

tation experiments (Brown et al., 2010). FMRP also interacts with two other ion channels, BK K$^+$ channels (Deng et al., 2013) and Ca$_V$2.2 (N-type) Ca^{2+} channels (Ferron et al., 2014).

The association of Slack with FMRP links the C terminus of the channel directly to mRNAs encoding proteins, such as Map1b and Arc, which are targets of FMRP (Fig. 4A). In brains from wild-type mice, but not those from Fmr1$^{-/y}$ mice that lack FMRP, these mRNAs can be coimmunoprecipitated with Slack channels (Brown et al., 2010). The Slack/FMRP interaction leads to a reversible activation of channel activity. Application of a recombinant fragment of FMRP(1–298) that includes most of the known FMRP protein–protein interaction domains to excised inside-out patches containing Slack channels causes a twofold to threefold increase in channel activity. This effect has been observed both for Slack channels expressed heterologously in *Xenopus* oocytes (Brown et al., 2010) and for native Na$^+$-activated K$^+$ channels in the bag cell neurons of *Aplysia*, where injection of FMRP produces a hyperpolarization of the membrane (Fig. 4B) (Zhang et al., 2012). A second effect of FMRP on the gating of Slack channels in both preparations is to largely eliminate subconductance states, which are readily detected before application of FMRP(1–298). No effect of FMRP(1–298) was detected on functional Slack channels that were truncated at their distal C terminus, the putative site of channel–FMRP interaction (Brown et al., 2010).

Slack and Slick are very widely expressed in central neurons (Bhattacharjee et al., 2002, 2005), and Na$^+$-activated K$^+$ currents have been characterized in a wide variety of neurons (Bhattacharjee et al., 2005; Kaczmarek, 2013). Suppression of Slack expression using siRNA techniques can reduce a major component of total K$^+$ current in several neuronal types (Budelli et al., 2009; Lu et al., 2010). One neuronal type that expresses Slack and in which the characteristics of the native Na$^+$-activated K$^+$ channels have been compared with those of Slack channels in heterologous expression systems is the principal neuron of the medial nucleus of the trapezoid body (Yang et al., 2007). These neurons fire at high rates with high temporal accuracy and are a component of the brainstem circuitry that determines the location of sounds in space (Kaczmarek et al., 2005). Increasing the level of Na$^+$-activated K$^+$ current in medial nucleus of the trapezoid body neurons in brainstem slices increases the temporal accuracy with which action potentials lock to stimulus pulses (Yang et al., 2007). The level of Na$^+$-activated K$^+$ current in medial nucleus of the trapezoid body neurons from Fmr1$^{-/y}$ mice is substantially reduced compared with that in neurons from wild-type animal, whereas no change in levels of Slack channels can be detected (Brown et al., 2010). This finding is consistent with the hypothesis that the interaction of Slack with FMRP in native neurons serves to enhance Na$^+$-activated K$^+$ current amplitude.

The interaction of an ion channel with part of the biochemical machinery that regulates translation of mRNAs suggests that changes in channel activity may contribute to the regulation of activity-dependent protein synthesis in neurons. Experiments testing this hypothesis are in progress. Circumstantial support for a role for Slack channels in the development of normal intellectual function has come, however, from the characterization of human mutations in the *Slack* gene (Barcia et al., 2012; Heron et al., 2012; Ishii et al., 2013; McTague et al., 2013; Martin et al., 2014; Milligan et al., 2014). Different mutations produce one of three types of seizures that occur in infancy or childhood: (1) malignant migrating partial seizures of infancy, (2) autosomal dominant nocturnal frontal lobe epilepsy, and (3) Ohtahara syndrome. Most of the mutations are in the large cytoplasmic C-terminal domain of Slack. The mutant channels conduct K$^+$

currents that are significantly greater than those of wild-type channels (Barcia et al., 2012; Martin et al., 2014; Milligan et al., 2014). In single-channel analysis, the mutant channels behave like channels that are constitutively activated by FMRP in that subconductance states are strongly suppressed or absent (Barcia et al., 2012).

Each of the human Slack mutations is associated with very severe intellectual disability and developmental delay (Kim and Kaczmarek, 2014). It is possible that these are a consequence of the abnormal electrical activity that occurs during the seizures. Nevertheless, the finding that autosomal dominant nocturnal frontal lobe epilepsy can be caused by mutations either in the neuronal nicotinic acetylcholine receptor or in Slack channels, but that intellectual disability only occurs for the Slack channel mutations (Heron et al., 2012), suggests that the disruption of the C-terminal protein–protein interactions of Slack with cytoplasmic signaling molecules contributes to the intellectual disability.

Perspectives

The encoding of information by patterns of neural activity demands that ion channel signaling exhibits a high degree of spatial and temporal precision. Molecular dissection of the ion channel proteome and detailed analyses of the functional impact of ion channel-associated proteins have greatly expanded our understanding of how such precision may be achieved. Moving forward, it will be important to consider that channel-interacting proteins may transform the biophysical features of ion channels in ways that could influence their pharmacological properties, as ion channels are major drug targets. Acknowledging that ion channels and their interacting proteins may have nonconducting roles, we may discover new and unexpected mechanisms by which disease-causing mutations lead to channelopathies. Finally, the potential of mapping ion channel proteomes in different neurons, and at distinct developmental time points, offers new perspectives on how ion channel regulation may be tailored to generate and maintain synapses and circuits.

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