Channels and transporters play essential biological roles primarily through the transportation of ions and small molecules that are required to maintain cellular activities across the biomembrane. Secondary to transportation, channels and transporters also integrate and coordinate biological functions at different levels, ranging from the subcellular (nm) to multicellular (μm) scales. This is underpinned by efficient functional coupling within molecular assemblies of channels, transporters, proteins, small molecules and lipids.

Molecular interactions create local microenvironments that, in some cases, uniquely modify the functional properties of the channels and transporters. These molecular assemblies built around a transporter or channel (“transportsomes” and “channelsomes”) can be considered as physiological functional units. In this special issue, we provide an overview of recent progress in our understanding of protein-protein and molecular interactions in transportsomes and channelsomes, which occur through both direct molecular contacts and more distal functional coupling, and examine the validity of these “somes”.

Subunit assembly is at the very basis of transportsomes and channelsomes. Nakajo and Kubo discuss the issue of their work on the interaction of the KCNQ1 pore-forming subunit with the KCNE auxiliary subunit of voltage-dependent K⁺ channels. The analysis of photo bleaching steps of single fluorescence protein-tagged K⁺ channel subunits suggests intriguing stoichiometric flexibility in the assembly of KCNQ1 and KCNE: multiple stoichiometries are allowed depending on the relative expression levels of the subunits. Different stoichiometries lead to functional variation of KCNQ1 channels, suggesting the importance of considering the relative quantities of the constituent proteins and molecules in channelsomes.

The physical and chemical nature of lipids surrounding the channel and transporter proteins in the membrane has a significant influence on the physiological function of channelsomes/transportsomes, as do protein-protein interactions. The importance of lipids is prominent in mechanosensitive channels such as TREK and TRAAK K⁺ channels, which are activated by shear stress and negative membrane pressure, as reviewed by Noël et al. who describe how polyunsaturated fatty acids including arachidonic acid and phospholipids are potent activators of TREK and TRAAK K⁺ channels. Protein-protein interaction strongly affects these properties of TREK such that association of A-kinase-anchoring protein AKAP150 fully activates the TREK current and abolishes its sensitivity to stimulation by mechanical stress and lipids. Proteins become associate with the membrane (and lipids within it) via their interactions with channel-forming subunit proteins, which infers the existence of functional units (channelsomes or transportsomes), and thus the importance of lipid rafts in the formation of these units, as discussed below.

Transient receptor potential proteins (TRPs) are rich in biology and chemistry. TRPs can naturally form a variety of channelsomes with distinctive roles. The review by Ong and Ambudkar illustrates that TRPC1 channelsomes, which act as a molecular machinery for store-operated Ca²⁺ channels (SOCs) activated by depletion of internal Ca²⁺ stored in the endoplasmic reticulum, are associated with cholesterol-binding scaffolding proteins such as caveolin-1 (Cav-1) in lipid raft domains. Assembly of the TRPC1 complex appears to be dynamic because rearrangement occurs during activation of SOCs by STIM: store depletion converts transient TRPC1 scaffolding by Cav-1 into a stable active STIM1-TRPC1 channel. Further examples are channelsomes for TRPC3, TRPC5, and TRPM2. These TRP complexes mediate Ca²⁺ influx and trigger activation of Ca²⁺-dependent signal transduction proteins to integrate and amplify characteristic receptor signals (Fig. 1). Thus, diverse and dynamic properties make TRP complexes particularly interesting for studies of channelsome biology.

We should reiterate that the primary aim of channelsome or transportsome formation is to ensure that the permeation and transportation of ions and small molecules across membranes are efficiently coupled to downstream events. Sites for this coupling can sometimes be observed with high-resolution microscopes as discrete subcellular structures, which should facilitate establishing biological relevance of these multi-protein units. The junctional membrane structure, which is the site for excitation-contraction (E-C) coupling in muscles (i.e., the coupling of surface membrane voltage-dependent Ca²⁺ channels (VDCCs) and sarcoplasmic reticulum ryanodine receptor Ca²⁺ release channels) falls into this category. Zhao et al. report that the junctional membrane structure is maintained by multiple mechanisms but,
The sites of vesicle fusion and the presynaptic membrane remains unresolved. Reflecting the essential roles played by VDCCs in controlling multiple neuronal processes, VDCCs form channelomes with several important regulatory proteins both up and downstream. Turner et al. describe protein complexes formed by VDCCs with G-protein-coupled receptors or Ca\(^{2+}\)-dependent K\(^+\) channels, which could enhance the efficiency of presynaptic control of neurotransmission and the regulation of membrane excitability. The bidirectionality of VDCC signaling may explain the characteristic ability of neurons to integrate information from numerous inputs. Precision in the formation of neural networks requires interactions between proteins both pre- and postsynaptically, and in the cleft. In addition to postsynaptic receptors, adhesion proteins and extracellular matrix proteins, VDCCs play an important role in interaction networks, and Nishimune comprehensively reviews this new type of VDCC channelsome.

Abnormalities in transportsomes and channelomes in diseases are also discussed in this special issue. Singer and Camargo describe the interactions between neutral amino acid SLC transporters and proteins such as angiotensin-converting enzyme (ACE) and their role in neurotransmission. Despite this complexity, junctophilin (discovered by Takeshima and colleagues) appears to play a central role in this process, where multiple membrane components are overlaid to form triad/diad junctions in muscles. It is important to note that the channelome formed by the interaction between VDCCs and ryanodine receptor Ca\(^{2+}\) release channels has served as a model mechanism in discussing activation of SOCs.

In a context similar to junctional membrane structures for E-C coupling, a discrete subcellular structure called the active zone (AZ) has been recognized as the site for excitation-secretion (E-S) coupling, making the presynaptic molecular complexes underlying E-S coupling another ideal target for channelome research. It is well known that various presynaptic proteins involved in the fusion of transmitter-containing vesicles with the presynaptic membrane are associated with VDCCs. Rab3-interacting molecules (RIMs) have emerged as AZ scaffolding proteins that link synaptic vesicles and depolarization-induced Ca\(^{2+}\) influx by interacting with Rab3 and VDCCs, respectively, at separate sites. (Fig. 2). The association of RIM-VDCC may provide important molecular insights into the mechanism by which VDCCs are geometrically related to the sites of vesicle fusion and the presynaptic membrane remains unresolved. Reflecting the essential roles played by VDCCs in controlling multiple neuronal processes, VDCCs form channelomes with several important regulatory proteins both up and downstream. Turner et al. describe protein complexes formed by VDCCs with G-protein-coupled receptors or Ca\(^{2+}\)-dependent K\(^+\) channels, which could enhance the efficiency of presynaptic control of neurotransmission and the regulation of membrane excitability. The bidirectionality of VDCC signaling may explain the characteristic ability of neurons to integrate information from numerous inputs. Precision in the formation of neural networks requires interactions between proteins both pre- and postsynaptically, and in the cleft. In addition to postsynaptic receptors, adhesion proteins and extracellular matrix proteins, VDCCs play an important role in interaction networks, and Nishimune comprehensively reviews this new type of VDCC channelsome.

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It is fascinating that the formation of channelosomes and transportosomes not only enhances signal transduction efficiency but is also implicated in pathogenesis. Original research by Wilson et al. demonstrates that the interaction of the axonal growth/guidance protein CRMP-2 (collapsing response mediator protein 2) with the N-type VDCC, Cav2.2, increases Cav2.2 translocation to the plasma membrane and that blockade of this interaction improves pain.31,32 This is reminiscent of ischemic neuronal death suppressed by the disruption of the NMDA receptor-PSD95-neuronal nitric oxide synthase complex.33 Disruption of channelosome/transportosome formation is a potentially powerful strategy for developing clinically relevant therapeutic tools. This special issue covers only a selection of important examples from among the vast number of transportosomes and channelosomes but is intended to enlighten readers as to their physiological importance. Compared to the straightforwardness of identifying transporter and channel molecules by cloning, the clarification of transportosomes and channelosomes is a laborious and slow process because of the complexity and heterogeneity of the interacting components and the dynamism with which they are multimerized. However, channelosomes/transportosomes offer significant signaling flexibility in the membrane at the interface between the internal and external environments, and this function clearly underlies some of the variability of cellular responsiveness seen among different types of cells/species. Realization of the importance of these complexes will give momentum to a rising field of research, a field that should be sufficiently diverse to engage scientists from many different biological disciplines.

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