Insights into the molecular foundations of electrical excitation

This is the era of the brain. Developing a deep understanding of the inner workings of this exceptionally complex organ and using that knowledge to invent new ways to affect its function is the premier scientific challenge of this century [1]. The fundamental currency of the brain and nervous system are electrical signals that orchestrate millisecond signaling through the networks of neurons that drive thought, feeling, and action. These rapid signals arise from a special class of transmembrane proteins called ion channels that control the transit of small ions across the cell membrane in response to diverse cues including changes in voltage, pressure, temperature, neurotransmitter binding, and intracellular signals [2,3]. Advances in the ability to interrogate ion channel molecular mechanisms have brought this field, once dominated by functional studies, to a level in which the full suite of structural, biophysical, and computational approaches can be used in concert with functional studies to dissect molecular mechanism [4,5]. This special issue of the *Journal of Molecular Biology* collects an exciting set of reviews and original research contributions that brings a slice of this fascinating field to the attention of readers.

Structural studies define the architectural underpinnings that are crucial for uncovering how channels function. As ion channels are complex allosteric proteins with many moving parts, defining atomic scale structures of ion channels, ion channel subunits, and ion channel modulators is at the heart and cutting edge of channel studies. Five of the reviews in this issue detail some of the exciting developments in structural studies of different classes of cation channels, which include the main drivers of neuronal electrical signals. Payandeh and Minor analyze the exceptional recent advances in structural studies of bacterial voltage-gated sodium channels, $BacNa_Vs$, and how these are shaping our understanding of their related eukaryotic voltage-gated sodium and calcium channel cousins [6]. Van Petegem covers advances in the structural understanding of the one of the largest characterized ion channels, the ryanodine receptor, and underscores the importance of integrated structural approaches for dissecting this intracellular calcium channel [7]. Kellenberger and Grutter describe structural and mechanistic advances in our understanding of two related channel types that share a common architecture in the face of little primary sequence similarly: P2X and acid sensitive ion channels (ASICs), and whose action is important for pain [8]. Many ion channel families have large intracellular domains that are crucial to their function and modulation. Morais-Cabral and Robertson delve into this issue for the KCNH family of potassium channels that have key roles in heart rhythm, cell cycle, and proliferation [9]. Finally, one of the most elegant channel systems to be outlined in structural detail recently is the so-called CRAC channel (calcium-release activated calcium channel) that is particularly important for calcium signaling in immune cells. This channel is formed from a multiprotein complex that when activated, bridges the plasma and endoplasmic reticulum membranes and is essential for the production of sustained calcium influx signals. Prakriya and colleagues outline what is known about this elegant molecular dance [10]. In addition to these cation channel reviews, two contributions deal with chloride channels. Accardi and colleagues review a relatively newly discovered class of calcium-activated chloride channels, Anoctamins, some of which may function as lipid scramblases, and the questions and controversies surrounding their function (Accardi et al, JMB, this issue). Riordan and colleagues provide new data on ways in which the effects of a well-known disease mutant that causes cystic fibrosis may be corrected [11].

The process of gating, the opening and closing of a transmembrane pore, is the fundamental event underlying channel activity. Tucker and colleagues review exciting ideas about how water and ions may behave in the narrow pores often found in ion channels and underscore the importance of molecular dynamics simulations for guiding hypothesis generation and the development of new ideas [12]. In an original contribution that further demonstrates the combined power of computational and experimental studies, Larsson, Noskov and colleagues examine how protons may be transported through the voltage-gated proton channel Hv1 that is important for macrophage activation (Chamberlin et al, JMB, this issue) [13]. Perhaps the ultimate experiment would be to watch the conformational changes of a single channel molecule as it transits between conductive and non-conductive states. Weatherill and Wallace outline the potential for and attempts at combining measurements of single channel activity, a method central to the ion channel field for more than 30 years [2,14], with experiments

designed to observe single molecule conformational changes to monitor simultaneously the activity and physical changes of a channel in action [15].

Finally, developing selective means to control ion channel function is essential for probing neuronal activity and informing efforts towards new ion channel-directed drugs to treat problems such as chronic pain. Natural products, particularly from venomous organisms, have been a rich source of ion channel pharmacology. Bosmans and colleagues offer a view into this complex world and highlight not only the mechanistic insights such probes can provide, but also the potential for screening and designing new and better ion channel modifiers that may be used as therapeutic agents [16]. Related to this topic, in an original research article, Kristersen and colleagues give new molecular insight into how a natural product from spider venom, ArgTX-636, blocks the function of a key class of glutamate receptor ion channels [17]. Highlighting a different strategy towards channel control, Subramayan and Colecraft outline achievements of rational engineering approaches as means to probe ion channel function, as a path towards biosensor development, and as a strategy for controlling channel activity in the complex milieu of an animal [18]. Along these lines, original research by Arnold and colleagues demonstrate how directed evolution of a member of the rhodopsin family of light-activated proton pumps widely used in optogenetics can be used to tune its spectral properties [19].

Ion channels have now fully entered the territory, once only the realm of the soluble proteins that historically constituted the core of studies reported in the *Journal of Molecular Biology,* in which structure, function, computational, rational engineering, and directed evolution are used to dissect, understand, and shape function. We anticipate that the contributions in this special issue will stimulate ideas in the field and attract further exciting reports to this venue.

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