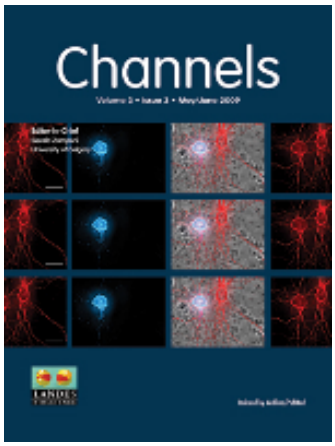

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Re-evaluating membrane transport processes: New insights and appreciation of protein behavior

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Commentary

Re-evaluating membrane transport processes

New insights and appreciation of protein behavior

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Key words: Transporter, exchanger, Na/K pump, potassium channel, chloride channel, symposium

The regulated, precise movement of ions across cellular membranes is essential for the integrity of various cellular processes and the long-term viability of all cell types. Such ionic movements are typically controlled by a variety of integral membrane proteins that may be classified into distinct categories, based on the biophysical properties of their transport activity; these include: ion channels, transporters and pumps. Operationally, ion channels may be viewed as "gated pores" that allow the transmembrane flux of a cation or anion down its electrochemical gradient. Such ionic movement is typically very rapid (i.e., 1,000,000 ions/sec or faster), and as a result, is capable of producing changes in membrane voltage on the order of milliseconds. Transporters, on the other hand, typically move an ion down its electrochemical gradient and then harness the free energy associated with this process to facilitate the transmembrane movement of another ion or organic molecule (i.e., glucose, bicarbonate, neurotransmitter) in either the same or opposite direction. In some instances, the movement of the co-transported substance may be against its cellular concentration gradient (i.e., Na/Ca exchange), thereby allowing a cell to either accumulate or export a given ion or compound. Mechanistically, transporters typically undergo a cycle of conformational changes or states, in which access to the substrate-binding sites on each site of the membrane is controlled by gates that sequentially open and close. Due to the mandatory coupling and coordination of these gates during the transport cycle, ion movement through transporters is typically 3–4 orders of magnitude slower than that of channels (i.e. 1000 ions/sec). In contrast to channels and transporters, ion pumps directly hydrolyze ATP and utilize the released energy to drive the transmembrane movement of one or more ions against its respective concentration gradient (i.e., Na/K pump). Interestingly, ATP hydrolysis is not an exclusive feature of ion pumps, as this process also utilized by some ion channel complexes (i.e., CFTR, KATP channels) to regulate the opening and closing of the ion-conductive pore.

What has emerged from the many years of detailed biophysical studies of membrane channels, transporters and pumps is an appreciation that these presumably "distinct" classes of proteins may in fact have specific features in common, which has led to a blurring of the operational boundaries initially established for these different models of substrate movement. For example, it is now evident that some ATP-dependent pump proteins can also behave as ion channels. In a recent symposium organized by Fran Ashcroft, David Gadsby and Chris Miller, participants presented and discussed a variety of different membrane transport phenomena, in which such hybrid behavior can be observed (i.e., neurotransmitter transporters, ATP-binding cassette (ABC)-containing proteins, Na/K pump, bacterial toxin channels and the CLC family of channels/transporters). One of the important messages to arise from this gathering is that such behavior is quite wide-spread amongst membrane transport proteins, and that these phenomena do not represent isolated biophysical curiosities. Now, in a series of 15, concise review articles prepared by participants at this conference, key aspects and new insights into the inner workings and transport capabilities of these different membrane complexes have been highlighted in a recent issue of The Philosophical Transactions of the Royal Society B. Collectively, these articles will help readers gain a stronger understanding and appreciation for these specific membrane transport phenomena, why they may be important physiologically, and how their dysfunction may contribute to pathophysiologic processes in cells and tissues.

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