Membrane transport proteins are crucial for life. They regulate the fluxes of ions, nutrients and other molecules across the membranes of all cells, and their activities underlie physiological processes as diverse as brain electrical activity, muscle contraction, water and solute transport in the kidney, hormone secretion and the immune response. Mutations in membrane transport proteins, or defects in their regulation, are responsible for many human diseases. Consequently, these proteins are targets for widely used therapeutic drugs.

Traditionally, membrane transport proteins have been divided into two groups: channels and transporters. Channels are membrane-spanning water-filled pores through which substrates passively diffuse down their electrochemical gradients whenever the regulatory gate is open. Transporters undergo a cycle of conformational changes linked to substrate binding and dissociation on opposite sides of the membrane. This conformational cycle can be coupled to energy sources like pre-existing ion gradients or ATP hydrolysis, thus allowing substrates to be moved ‘uphill’ against their concentration gradients, as in nutrient and ion accumulation into the cell or export from the cell of ions, drugs or xenobiotics.

All transporters must effectively have two ‘gates’ that control access from either side of the membrane to the substrate-binding sites as well as a conformational cycle that prevents both these gates from being open at the same time. It is obvious that if both gates were open simultaneously, the protein would then operate as a channel. And, owing to the orders-of-magnitude higher flow rates through channels than through transporters, even a fleeting moment of channel-like behaviour would render a transporter useless. To obviate any such occurrence, the conformational cycles of many transporters incorporate occluded states in which both gates are shut, enclosing the bound substrate, before one of the gates opens to release it.

However, it has been apparent for some time that a rigid distinction between channels and transporters is no longer tenable, and a more nuanced view is called for. Before his untimely death from a climbing accident, Peter Läuger spelled out theoretically how accidental gate opening could be coupled to energy sources like pre-existing ion gradients or ATP hydrolysis to translocate diverse substrates across cell membranes. It has long been recognized that the sulphonylurea receptor SUR and the cystic fibrosis transmembrane conductance regulator CFTR are exceptional among ABC proteins in that they do not serve as pumps. Instead, they have hijacked the ATP-binding and hydrolytic activity of the nucleotide-binding domains (NBDs) to gate an intrinsic chloride channel (CFTR) or to regulate the gating of a separate inward-rectifier potassium channel (SUR).

Recent crystal structures of bacterial ABC transporters have suggested a common molecular mechanism by which binding and hydrolysis of ATP are coupled to conformational changes in the membrane-spanning domains, as discussed by Locher (2009). Muallem & Vergani (2009) consider how the structural changes occurring at the NBDs of CFTR open and close the chloride channel contained within its membrane domain. The paper by Aittoniemi et al. (2009) focuses on how SUR regulates the activity of the pancreatic beta-cell K_ATP channels and how failure of this regulation by naturally occurring mutations gives rise to human
disease. Nelson et al. (2009) present a novel tool—a knockout/wild-type chimeric mouse—for analysing the role of the $K_{\text{ATP}}$ channel in cardiac stress tolerance.

**Neurotransmitter transporters**

After neuronal electrical activity, the synaptic cleft must be cleared of released neurotransmitters, such as glutamate, noradrenaline, serotonin and GABA. This is achieved by a class of sodium-coupled cotransporters that use the energy stored in the pre-existing sodium gradient across the membrane. Many of these transporters have a parallel ion leak that is somehow gated by the transported substrate. X-ray crystal structures of prokaryotic homologues of these sodium-coupled transporters are described by Gouaux (2009) and the coupling of an intrinsic chloride leak to glutamate uptake in the EEA1 transporters is covered by Holley & Kavanaugh (2009). Prasad et al. (2009) discuss the effects of disrupted transporter function in relation to mental disease.

In an analogous way, Ellory et al. (2009) describe how a human disease arises from mutations that produce an uncoupled conductance in the chloride–bicarbonate exchanger AE1 that normally does not generate any transmembrane current. The dipeptide transporter described by Meredith (2009) is another example of a transporter that similarly may contain an ion channel.

**The CLC family**

The CLC proteins, originally thought to be a family of chloride channels, are now recognized to include both channels and chloride–proton antiporters: for example, of the nine CLCs in the human genome, four are channels and five are antiporters. However, both types of the CLCs, in which a protein long thought to be an ion channel, anthrax toxin, actually functions as a pump that uses a proton gradient to inject a lethal enzyme into the cytoplasm of the unfortunate target cell.

**SUMMARY**

As an intrinsic part of their molecular mechanisms, transporters may harbour channels within them. By disrupting one gate or the communication between gates (so that both are sometimes open simultaneously), a transporter can be converted into a channel. It is natural to envision that this is how mutations and toxins produce channels from transporters. In addition, by eventually losing a gate through evolution, a transporter could become a channel: for example, this may be how an ABC protein like CFTR became a channel gated by ATP binding and hydrolysis. Likewise, the CLC channels may be ‘broken’ CLC transporters. Whether any transporters have been transmuted from channels by growing an additional gate is less certain, but one example might be the Kdp-ATPase, a bacterial K pump proposed to have evolved from a K channel.

Although it has not been reported, the examples presented in this issue make us wonder whether some proteins can flip between pump and channel mode under physiological conditions. Another question is whether proteins of intermediate function exist. Do leaky transporters occur naturally, in which the gates are uncoordinated normally or become so in response to regulatory agents, rather than as a pathological result of mutations or toxins? Such slippage could be of value to the cell, for example as a means of controlling solute gradients. We are not aware of any evidence for such a thing but it seems theoretically plausible.

The above discussion cites examples of proteins that function as either a channel or a transporter, or as something intermediate between these two ends of the spectrum. However, there are also proteins in which both channel and transporter operate at the same time. This situation has been most thoroughly studied in glutamate and other neurotransmitter transporters, but our understanding of how this feat is achieved is still quite vague.

So how do you tell whether your favourite flux is mediated by a channel or a transporter? The question is easy to pose but difficult to answer rigorously, and it has caused many headaches among membrane biophysicists. Experimentally, the unitary flux rate is most commonly used to make this distinction. Typically, channels are fast (greater than $10^6$ s$^{-1}$) and transporters are slow (1–1000 s$^{-1}$). These rates reflect the very different energy barriers of the limiting steps in the two types of substrate movement: low for diffusion (when all gates are open) and high for conformational rearrangements (alternating gating). But this distinction is not foolproof as there are low-conductance channels and there may be high-turnover transporters. Ultimately, atomic-resolution structural information, in multiple conformations, is required to understand a given

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transport mechanism. After a long wait, such structures are now beginning to enrich the membrane transport field. Thus, it seems likely that during the next few years new structural insights will illuminate the ambiguous interface between channels and transporters.

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