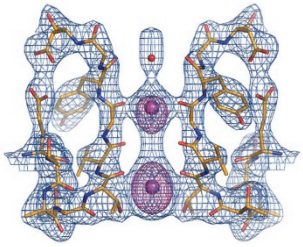
Structuring selectivity



Potassium channels show amazing discrimination, favoring K^+ over other monovalent cations, such as Na^+ and Li^+. Although structural and functional studies have revealed much about the KcsA channel, including the residues physically involved in ion permeation and the conformational changes involved in channel opening, the basis for ion selectivity is still an open question. Now, MacKinnon and colleagues have used isothermal titration calorimetry (ITC) and new structural data to investigate how ions are selected by KcsA and the contributions they make in promoting the conductive state. ITC experiments using different monovalent and divalent cations, combined with the crystal structure of a KcsA mutant trapped in a nonconductive state, suggest that the heat measured upon K^+ binding is correlated with the conformational change from the nonconductive to the conductive state. Furthermore, the authors implicate the ionic radius as an important determinant of K^+ channel selectivity, as both monovalent and divalent cations similar in size or larger than K^+, such as Cs^+, Rb^+ and Ba^{2+}, bind within the channel, whereas those with radii similar to or smaller than Na^+, including Li^+ and Ca^{2+}, do not. A crystal structure of KcsA with Ba^{2+} bound at the selectivity filter supports the correlation between size-selective binding and adoption of the channel's conductive state. Thus, the K^+-dependent conformational change is a form of selectivity, occurring only when an ion of appropriate size binds. This is consistent with the 'snug-fit' hypothesis of Hille and Armstrong, proposed over 30 years ago. (*PLoS Biol.* **5**, e121, 2007) *MM*

Syts throw a curve

Membrane–SNARE protein interactions are key to rapid vesicle fusion and neurotransmitter release upon Ca^{2+} influx. Synaptotagmin-1 (Syt1) is the Ca^{2+}-sensing component of SNARE-dependent fusion, but it has not been completely clear how Ca^{2+} binding to Syt1 results in membrane fusion. McMahon and colleagues have now found that in the presence of Ca^{2+}, Syt1, as well as other synaptotagmins, can induce curvature in target membranes (as assessed by ability to induce membrane tubules). This Ca^{2+}-dependent induction of membrane curvature requires that the two Syt1 Ca^{2+}-binding domains, C2A and C2B, be linked. Mutagenesis revealed that two hydrophobic residues on the C2A domain and two on the C2B domain, previously shown to insert into target membranes, are required for curvature induction. The mutant constructs showed a correlation between the ability to induce curvature and the ability to promote SNARE-dependent liposome fusion. However, not all constructs that promote tubulation can trigger SNARE-dependent fusion, suggesting that induction of a curved membrane is not sufficient to facilitate fusion but that additional SNARE interactions are crucial for coupling membrane-curvature induction with SNARE-mediated fusion. Together, these observations suggest that upon Ca^{2+} binding, synaptotagmins induce local membrane curvature, an effect predicted to reduce the activation barrier for subsequent membrane fusion, thus linking the previously observed Ca^{2+}-sensing activity of Syt1 with its ability to promote vesicle fusion. Further studies can now be directed to testing this model *in vivo*. (*Science*, published online 3 May 2007, doi:10.1126/science.1142614) *SL*

Research Highlights written by Inês Chen, Boyana Konforti, Sabbi Lall and Michelle Montoya.

When small differences matter

Prion proteins have a number of unique properties. They can switch to a conformation that is self-perpetuating and therefore infectious and have the ability to form related but structurally distinct conformations, or strains, that confer unique phenotypes. Prion proteins of different species cannot easily transmit the prion state between species. In both yeast and mammals, the ability of prions to establish and overcome species barriers is somehow related to their ability to form distinct strains, but how is not understood. Using surface-bound prion peptide arrays, Tessier and Lindquist have found that the yeast prion Sup35 interacts with a small subset of peptides that can lead to conversion of Sup35 to a self-templating state. A homologous Sup35 prion domain from *Candida albicans*, a species separated from *Saccharomyces cerevisiae* by over 800 million years, behaves similarly. Examining a promiscuous *S. cerevisiae*/*C. albicans* prion chimera that has previously been shown to cross the species barrier reveals that it can interact specifically with peptide-recognition elements from both species. Thus, the same peptide sequence that controls conversion of the nonprion conformation into the prion state is also responsible for the formation of distinct prion strains and the species barrier. Thus, conversion of prions into distinct strains depends on subtle differences between small, specific recognition elements. More broadly, these findings suggest that at least these two prion proteins fold very differently from most other proteins, in which folding is driven by a large number of intramolecular interactions. Instead, for these prions, folding is driven by intermolecular interactions between very small sequence elements. Whether this holds true for other amyloidogenic proteins remains to be determined. (*Nature*, advance online publication 9 May 2007, doi:10.1038/nature05848) *BK*

Sensing the phagosome

PhoQ participates in the regulation of virulence genes in *Salmonella* spp. and other bacteria, and spans the inner bacterial membrane, with its kinase domain in the cytoplasm and its sensor domain in the periplasm. Activation of PhoQ occurs when *Salmonella* enters the phagosome of host cells, but the activation trigger was previously unclear. Divalent cations are known to repress PhoQ, whereas antimicrobial peptides can activate it, presumably by displacing the divalent cations and relieving repression. Using NMR spectroscopy, Miller and colleagues have recently discovered that PhoQ's sensor domain undergoes conformational changes when exposed to pH 5.5, with a histidine residue in the structural core of the domain playing a central role in the switch. In fact, certain mutations of this residue result in derepression at neutral pH and changes in the NMR spectrum similar to those seen with wild-type PhoQ at low pH. Acidic pH and the presence of antimicrobial peptides have additive effects on PhoQ activity, suggesting that these signals are sensed through distinct mechanisms and act together to fully activate PhoQ. Interestingly, both conditions are encountered by *Salmonella* inside the host cell phagosome. Divalent cations seem to stabilize the folds of several flexible regions and limit PhoQ's response to the signals. Although future research should reveal how the conformational changes in the sensor domain are transmitted to the kinase domain, the work described by Miller and colleagues elucidates what PhoQ senses.
(*Mol. Cell* **26**, 165–174, 2007) *IC*