of downstream signalling. However, Sanada and Tsai found that a GPCR-independent activator of G proteins, AGS3, was important for establishing the axis of division in cortical progenitors. AGS3 is expressed by cortical progenitors in mouse embryos, and silencing its expression causes abnormalities in the mitotic spindle orientation that are similar to those caused by disruption of Gβγ signalling.

This elegant study provides the first direct evidence for the molecular mechanism that regulates mitotic spindle orientation in cortical progenitor cells. It will lead to new ways of deciphering the complex events that trigger changes in cell-cleavage plane orientation and asymmetric cell fate choices during neurogenesis.

Jane Qiu

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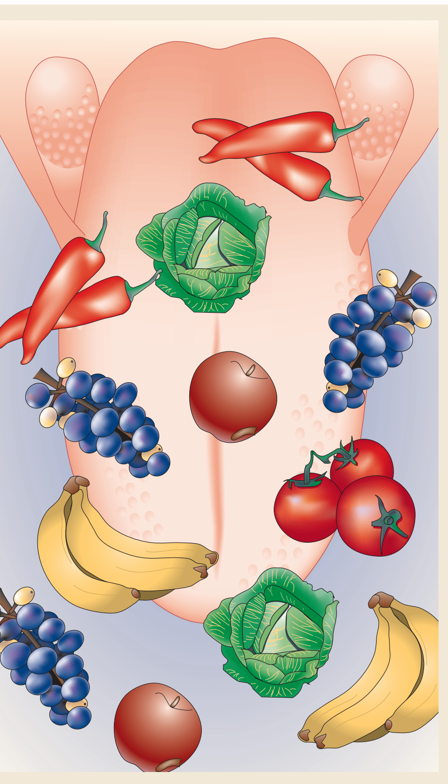
WEB SITE

Tsai's laboratory: http://www.hms.harvard.edu/dms/bbs/fac/tsai.html



ION CHANNEL STRUCTURE

Switching on to potassium channels

Our knowledge of the structure of voltage-dependent K^+ (Kv) channels, which shape the neuronal action potential, has come largely from studies of prokaryotic channels, which can be expressed at high levels in *Escherichia coli*. Now the crystal structure of a mammalian Kv channel has been published, providing important insights into how the structural features of these channels allow them to operate in eukaryotic cells.

Eukaryotic Kv channels are very similar to their prokaryotic counterparts. For example, the sequence of the selectivity filter — the part of the channel that confers specificity for K^+ — is highly conserved and is likely to produce a similar structure in all K^+ channels. But eukaryotic channels also have some unique features. To gain a better understanding of the structural basis of Kv channel function in eukaryotes, the researchers, led by Rod MacKinnon, chose to investigate Kv1.2, a member of the *Shaker* family of K^+ channels.

To obtain crystals of Kv1.2 in its native arrangement, the group used a mixture of lipids and detergent during purification and crystallization. This clever approach helped to compensate for removal of the lipid membrane during isolation of the channel, keeping the voltage sensors correctly positioned with respect to the channel pore. The channel was crystallized in a complex with an oxidoreductase β-subunit, an auxiliary protein that might regulate mammalian Kv channels in their natural environment.

The amino terminus of Kv1.2 is known to form a 'T1' domain inside the cell, which is located over the pore entrance to the cytoplasm. This domain serves as a binding site for the β-subunit, which is thought to be involved in the process of channel inactivation. Long *et al.* found that the relationships between the membrane-spanning components of Kv1.2, the intracellular T1 domain and the β-subunit were consistent with functional studies of inactivation gating in *Shaker* channels. Interestingly, the structure also pointed to a possible role of the β-subunit as a redox sensor, coupling the redox state of the cell to activity of the channel.

Kv1.2 was crystallized with the pore in the open conformation. Because the normal conformation of the voltage sensors was preserved in this structure, Long *et al.* were able to take a closer look at the way in which the voltage sensor 'paddles', which move through the membrane in response to voltage changes, open and close the pore. They found that the voltage sensors are almost independent domains inside the membrane, being only weakly attached to the pore through 'linker' helices. The positioning of arginine residues in the voltage sensor suggested that a balance between electrostatic and hydrophobic forces is central to the way in which the sensor performs mechanical work on the pore.

The hope is that these fascinating insights into the structure of a mammalian Kv channel in the open conformation will soon be followed by a view of the switch in its closed state.

Rebecca Craven

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