

Gating ring strengthens marriage of BK channel voltage sensing to pore opening

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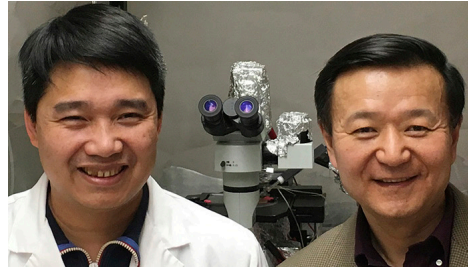
A new *JGP* study shows that the gating ring helps the voltage-sensing domain open the BK channel's pore.

Researchers have long struggled to understand how the structural features of ion channels are linked to their behavioral properties. In their paper published this month in *The Journal of General Physiology*, Zhang et al. provide new information on how the behavior of BK channels is regulated (1).

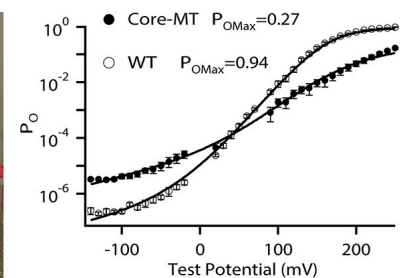
BK channels pass large potassium (K^+) currents across the cell membrane to maintain the electrochemical balance in excitable cells. They are composed of four identical α subunits, called mSlo1, accompanied by different modulatory β subunits. mSlo1 contains three distinct domains: a membrane-spanning pore-gate domain, a transmembrane voltage-sensing domain (VSD), and a cytoplasmic domain containing binding sites for calcium ions. This cytoplasmic domain joins with those of the other mSlo1 subunits to form a structure called the gating ring. Accordingly, mSlo1 channels will open either in response to shifts in membrane voltage or to binding of calcium at the gating ring (2). Calcium binding can also enhance voltage-driven channel activity and vice versa (3).

"The mechanism by which calcium binding and voltage-dependent channel activation affect each other was unclear," says Jianmin Cui, a Professor at Washington University in St. Louis, "but we were inspired by a recent paper which showed that mSlo1 channels lacking their gating ring lost sensitivity to calcium but remained voltage dependent."

Cui's group, led by research scientist Guohui Zhang, collaborated with the authors of that paper (4) to learn more about how gating ring loss affects the channel's gating behavior. When the channel lacking its gating ring, Core-MT, was expressed in *Xenopus laevis* oocytes, it behaved similarly to the wild-type channel in the absence of Ca^{2+} : like a voltage-activated K^+ channel. Tiny currents, called gating currents, were caused when Core-MT's VSD underwent conformational changes



Guohui Zhang (left), Jianmin Cui (right), and colleagues show that removal of the gating ring from mSlo1 channels dramatically changes the channels' open probability (P_o , above), even though their voltage-sensing domains respond normally to membrane voltage (not depicted). PHOTO COURTESY OF THE AUTHORS.



in response to rising membrane voltage and were detectable at slightly lower voltages, but otherwise resembled those of the wild-type channel. However, consistent with the previous work on Core-MT, the mutant channel required higher voltages than wild type before K^+ currents started flowing through it. In fact, high voltages disrupted cells' membranes before maximal currents could be observed.

An earlier study by Zhang and Cui had identified a pair of mutations in wild-type mSlo1 channels' pore-gate domain that allow the channel to open at lower voltages (5). When these same mutations were inserted into Core-MT, they enabled the induction of maximal K^+ currents. Combined with measurements from patch-clamped individual channels, the authors were able to show that, even at its maximum, Core-MT has a much lower open probability than wild type.

"Deleting the gating ring...changes the interaction between the voltage sensor and the pore."

Interestingly, mSlo1 channels will also open stochastically at negative membrane voltages even though the VSD is at rest, and Zhang et al. observed that Core-MT was more likely to open than wild type under these conditions. Together, these data indicate that, although the Core-MT channel's VSD responds normally to changes in

membrane voltage by undergoing a conformational change, this change is not effectively communicated to the channel's pore-gate domain; in the absence of the gating ring, the VSD fails to induce channel opening at positive voltages and can't keep the channel shut at negative ones.

An earlier study modeling the gating behavior of BK channels (6) had already suggested that conformational shifts in the VSD do not directly force the pore-gate open, but merely make pore opening more likely. Zhang et al. have extended this model with the observation that the cytoplasmic gating ring helps communicate VSD structural shifts to the channel pore.

"Deleting the gating ring doesn't change how the voltage sensor works, but it changes the interaction between the voltage sensor and the pore," explains Cui. How the gating ring couples VSD conformational changes to the pore-gate domain is still unknown, but Cui notes that recent structural studies have opened the door to a better understanding of the physical relationship between these two domains.

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