Identification of Weak interactions which determine gating of Kir2 channels

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Abstract: Kir2.1 channel, one kind of transmembrane protein of inwardly rectification potassium (Kir) channels, can regulate the resting membrane potential and shape electrical signals in the heart and in neurons. Kir2.1 channel is activated by phosphatidylinositol 4,5-bisphosphate (PIP_2) alone. However, the detailed PIP_2-induced gating mechanism is far from clear.

In the present work, we have combined molecular dynamics (MD) with targeted MD simulations to address the conformational transition pathway in the gating of the Kir2.1 channel. Our data show that Kir2.1 channel gating unfolds in a step-by-step process with change of weak interactions. First, with the upward motion of the cytoplasmic domain (CTD), the C linker forms a new helix, named slide helix, and the interaction between slide helix and lipid is strengthened. The interlocking weak interactions between the lipid, slide helix, outer transmembrane helix (M1) and outer transmembrane helix (M2) contribute to the M2 helix bend. Second, the kink of the C-linker triggers the rotation of the CTD which reshapes two weak interaction-networks. ①The weak interactions between G loop and CD loop are weakened, which releases the G-loop. ②The interlocking weak interactions between N-terminus, CD loop, C linker and G loop, which are strengthened and will stabilize the G loop gate in the open state.

The weak interaction networks control the PIP_2-induced conformational changes during Kir channels gating. Based on the data, a brand new gating model is proposed which will shed light on understanding the molecular mechanism of PIP_2 gating of Kir channels.

Ref.

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