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STRUCTURAL BASIS FOR LIPID-DEPENDENT GATING OF A KV CHANNEL

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Lipid-dependent gating refers to our observations that lipid molecules without phosphate groups in their headgroup regions, called nonphospholipids, favor the resting state of the voltage-sensor domain in a voltage-gated potassium (Kv) channel whereas phospholipid molecules favor the activated state. More studies suggest that the annular lipids and a Kv channel form a functional unit and both nonspecific and specific interactions at the protein-lipid interface contribute to the energetic differences of the channel in different gating states. Since our discovery of the phenomenon in KvAP, similar results have been obtained from other voltage-gated ion channels in both *in vitro* and *ex vivo* systems, suggesting that the lipid-dependent gating could be a more generic gating mode for other voltage-gated ion channels. To analyze the conformational changes of a Kv channel in different lipids, we obtained a peptide-binder that recognizes a non-phospholipid-stabilized resting state of the KvAP voltage sensor and found that attachment of the peptide to the C-terminus of the channel appears to keep it in the resting state in phospholipid membranes. We analyzed the structure of the KvAP-peptide fusion protein by single particle cryoEM and revealed a voltage-sensor ring that may keep the voltage-sensor paddle in a resting state where all its arginine residues face the intracellular side of the gating pore with the tip of the S3S4 paddle leaning against the splayed-open S1/S2. The structural features of the new model are different from the four-helix bundle structure of the voltage sensor domain in the activated conformation and allow the S3/S4 to face annular lipids directly. Such structural arrangements could explain a set of biochemical data we obtained from different channel mutants and reveal new insights on the possible movement of the voltage sensor domain to achieve its gating control of the ion-conducting pore. Another surprise from the cryoEM study is that an unknown protein binds tightly to the extracellular side of the KvAP pore domain. MS spectrometry and proteomic analysis suggested a few candidates that need further characterization. We are investigating whether the new pore-binders play a role in the lipid or voltage-dependent gating of the channel.