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CryoEM Structure of a Vascular KATP Channel in the Presence of Activating Mg-Nucleotides

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Vascular tone is dependent on smooth muscle KATP channels comprising pore-forming Kir6.1 and regulatory SUR2B subunits, in which mutations cause Cantú syndrome. Unique among KATP isoforms, they lack spontaneous activity and require Mg-nucleotides for activation. Previously our group reported cryoEM structures of a vascular KATP channel determined in the presence of ATP and the antagonist glibenclamide. We showed that the cytosolic domain of Kir6.1 is untethered from the membrane in contrast to Kir6.2 in the pancreatic Kir6.2-SUR1 channel determined under the same condition, and that SUR2B subunits adopt distinct rotational “propeller” and “quatrefoil” geometries surrounding their Kir6.1 core. However, structural mechanisms underlying Mg-nucleotides induced NBD dimerization and associated conformational changes toward channel activation are unknown. Here we present the cryo-EM structure of a vascular KATP channel determined in the presence of Mg-AMPPNP and absence of additional PIP2. The structure has a quatrefoil appearance and the two nucleotide binding domains (s) of SUR2B are dimerized. Interestingly, the cytosolic domain of Kir6.1 is tethered to the membrane even with no PIP2 added to the protein sample, suggesting NBD dimerization is preconditioning CTD of Kir6.1 for PIP2 interaction and channel opening. The structures captured implicate a progression of intermediate states toward channel activation and explain the essential role of Mg-nucleotides in vascular KATP channel activity.