P(3,5)P2 lipid binding-induced activation of the human two-pore channel 2

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Two Pore Channels (TPCs) are intracellular ion channels that are widely expressed in eukaryotic cells. Depending on the host cell, they are involved in diverse processes like the cellular cation and pH homeostasis, Ebola virus infection and cancer cell migration. The gating mechanism and regulation of these channels are therefore of strong interest. It was shown that TPC1 of Arabidopsis thaliana gets activated in a Ca2+ and voltage dependent manner. Furthermore, patch-clamp experiments with wild type and truncated variants demonstrated that the C-terminus of AtTPC1 is an indispensable player for channel activity. In contrast, the homologous TPC2 of humans is gated open upon addition of phosphoinositides (PI(3,5)P2), however, the exact binding site and the relation to channel activation are unknown. To investigate the mode of channel activation of AtTPC1 and hTPC2 we combined experimental techniques and molecular dynamics simulations at the coarse-grained and atomistic level. Results demonstrated that AtTPC1 subunits interact via their C-terminal regions, and PI(3,5)P2 lipids tend to bind to predominately positively charged sub-regions of hTPC2. Further experiments will show if these homologues share common features in the gating mechanism.