Structures and Mechanisms of the Two-Pore Channel TPC1 from Arabidopsis thaliana

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Two-pore channels (TPCs) contain two copies of a Shaker-like six-transmembrane (6-TM) domain in each subunit and are ubiquitously expressed in both animals and plants as organellar cation channels. Arabidopsis TPC1 (AtTPC1) is localized to the vacuolar membrane and is responsible for generating the slow vacuolar (SV) current. AtTPC1 is a voltage-gated Ca^{2+}-modulated Ca^{2+}-permeable non-selective cation channel. We performed structural and electrophysiological studies of AtTPC1. AtTPC1 activation requires both voltage and cytosolic Ca^{2+}. Ca^{2+} binding to the cytosolic EF-hand domain triggers conformational changes coupled to the pair of pore-lining inner helices from the first 6-TM domains, whereas membrane potential only activates the second voltage-sensing domain, the conformational changes of which are coupled to the pair of inner helices from the second 6-TM domains. Luminal Ca^{2+} or Ba^{2+} can modulate voltage activation by stabilizing the second voltage-sensing domain in the resting state and shift voltage activation towards more positive potentials. The Ba^{2+}-bound AtTPC1 structure reveals a voltage sensor in the resting state, providing structural insight into the general voltage-gating mechanism among voltage-gated channels.