Channel-like voltage sensor operates in an enzyme: a novel membrane protein coupled with membrane potential changes

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It has been well established that primary role of cellular electrical signal is to change ion fluxes via ion channels and transporters, leading to alteration of intracellular chemical conditions. However, other signaling pathways coupled with membrane potential have not been fully elucidated. I will talk about a novel membrane protein from an ascidian (*Ciona intestinalis*), one of marine sessile invertebrates, which contains an ion channel-like voltage sensor and phosphatase domain similar to PTEN, a tumor suppressor protein. This protein is denoted as VSP (voltage sensor-containing phosphatase). The C-terminal enzyme domain of this protein shows the robust activity of dephosphorylating phosphatidylinositol (3,4,5) trisphosphate, which is known to play a critical role in regulating cell morphology, chemotaxis, apoptosis and cell proliferation. Channel-like domain exhibits robust asymmetrical charge movements that resemble gating currents of voltage-gated channels. We provide evidence that the enzymatic activity of VSP changes with membrane potential through the conformational change of the voltage sensor. This protein provides a completely novel pathway of cell signaling by which an electrical signal is transduced into biochemical signals without requiring ionic flow. This also gives the first example in which enzymatic activity is regulated by membrane potential through the operation of channel-like voltage sensor, potentially providing a new platform to understand structure-function basis for coupling between voltage sensor and its effector. The presence of orthologous genes in genomes of teleosts and mammals also suggests conserved physiological role throughout chordates.