Interaction between S4 and the phosphatase domain mediates electrochemical coupling in voltage-sensing phosphatase (VSP)

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Natsuki Mizutani, Akira Kawanabe, Yuka Jinno, Hirotaka Narita, Tomoko Yonezawa, Atsushi Nakagawa, and Yasushi Okamura

Electrical signals in the nervous system are mediated by voltage-gated ion channels (VGICs). VGIC consists of a voltage sensor domain (VSD) and an ion permeation pore, and regulates an ionic flow through the plasma membrane in response to membrane potential change. The fourth transmembrane segment of the VSD (S4) senses membrane potential change. Interestingly, voltage-sensing phosphatase (VSP) has a VSD similar to that of VGICs but does not have an ion permeation pore. Instead, the VSD regulates the cytoplasmic catalytic region with structural similarity to PTEN, a tumor suppressor enzyme, exhibiting the voltage-dependent phosphoinositide phosphatase activity which is important for regulation of sperm motility. However, it remains unclear how an electrical signal is converted into a chemical one. In this study, using a fluorescent unnatural amino acid [3-(6-acetylnaphthalen-2-ylamino)-2-aminopropanoic acid (Anap)] we found that hydrophobic residues at the C-terminal end of S4 play a critical role in the signal conversion through a direct interaction with a hydrophobic part of the phosphatase domain called the hydrophobic spine. Similar hydrophobic part is well conserved in PTEN and other phosphoinositide phosphatases. The predicted full-length structure of *Ciona intestinalis* VSP also supports this interaction. Taken together, the interaction of S4 with the hydrophobic spine mediates the conversion from an electrical signal to a chemical one in VSP. Our findings might help to understand the mechanisms how the VSD regulates an ionic flow in VGICs, which relate to various diseases such as arrhythmia and epilepsy.

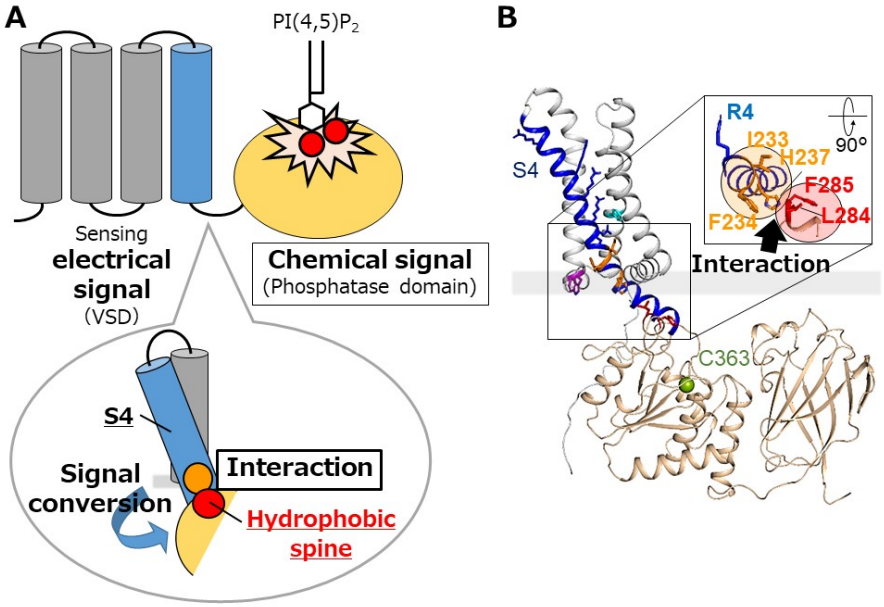

Figure. Mechanisms underlying the signal conversion in VSP.

(A) Cartoon of VSP. (B) Predicted full-length structure of *Ciona intestinalis* VSP.