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LES SÉMINAIRES DE L'INMG

Coupling from electric signal to lipid signal; voltage-sensing phosphoinositide phosphatase

par

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Abstract :

Biological membranes have dual roles in cell signaling: insulator for electrical signal by transfer of ion across membrane as well as the place for metabolism for production of lipid mediators such as arachidonic acids or phosphophositides. These two signals interact with each other through changes of ion concentration, mainly intracellular calcium ions, by the concerted activities of ion channels, transporters and GPCRs. There is a rare case where single membrane proteins directly link between electrical signal and lipid-mediated cell signaling. Voltage-sensing phosphatase consists of the ion channel like voltage sensor and PTEN-like phosphoinositide enzyme. In VSP, single voltage sensor regulates the downstream enzyme and the phosphoinositide phosphatase activity is activated by membrane depolarization leading to depletion of mainly PI(4,5)P2. Substrate specificity of VSP is more broad than PTEN; VSP shows both of 3-phosphatase activity and 5-phosphatase activity unlike PTEN which shows the rigid selectivity toward 3-phosphate of the inositol ring of PI(3,4,5)P3 and PI(3,4)P2. However, the key question how transmembrane voltage sensor regulates the cytoplasmic enzyme has remained unanswered, mainly because a method of detecting structural change in the cytoplasmic region has been limited. We have recently applied a method of genetical incorporation of fluorescent unnatural amino acid, Anap, to the cytoplasmic region of Ci-VSP (sea squirt *Ciona intestinalis* VSP) which was expressed in Xenopus oocyte. This method enables detection of fine structural change reported by fluorescence intensitiy without perturbing the local protein structure. Voltage-dependent fluorescence change of Anap showed two bidirectional changes along the voltage, decrease at low membrane depolarization and increase at higher depolarization, suggesting that the structure of the cytoplasmic region takes multiple conformations. By applying the method to different constructs of Ci-VSP with altered enzyme activity, we obtained evidence that the enzyme takes at least two activated states with distinct magnitude of enzyme activity. Given that voltage sensor of Ci-VSP takes multiple states during activation, it will be intriguing to see in the future how individual enzyme states correlate with states of the voltage sensor.

Selected Publications:

1. *Okamura Y, Kawanabe A, Kawai T. (2018) Voltage-Sensing Phosphatases: Biophysics, Physiology and Engineering. ***Physiological reviews*** in press.

2. *Sakata S, Jinno Y, Kawanabe A, *Okamura Y.(2016) Voltage-dependent motion of the catalytic region of voltage-sensing phosphatase monitored by a fluorescent amino acid. ***Proc. Natl. Acad. Sci. U. S. A.*** 113(27):7521-7526.

3. Matsuda M, Takeshita K, Kurokawa T, Sakata S, Suzuki M, Yamashita E, *Okamura Y, *Nakagawa A (2011) Crystal structure of the cytoplasmic PTEN-like region of Ci-VSP provides insight into substrate specificity and redox regulation of the phosphoinositide phosphatase activity.***The Journal of Biological Chemistry***, 286(26):23368-77.

4. Sakata S, Hossain MI, *Okamura Y (2011) Coupling of the phosphatase activity of Ci-VSP to its voltage sensor activity over the entire range of voltage sensitivity. ***The Journal of Physiology***, 589(11):2687-705.

5. Iwasaki H, Murata Y, Kim Y, Hossain MI, Worby CA, Dixon JE, McCormack T, Sasaki T & * Okamura, Y (2008). A voltage-sensing phosphatase, Ci-VSP, which shares sequence identity with PTEN, dephosphorylates phosphatidylinositol 4,5-bisphosphate. ***Proc Natl Acad Sci U S A*** 105, 7970-7975.

6. Murata Y, Iwasaki H, Sasaki M, Inaba K & *Okamura Y. (2005). Phosphoinositide phosphatase activity coupled to an intrinsic voltage sensor. ***Nature***, 435:1239-1243.