Structural and biophysical studies of IP3 receptor (IP3R): Toward understanding the regulatory mechanism

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Inositol 1,4,5-trisphosphate receptor (IP3R) is an IP3-gated Ca2+ release channel on the ER membrane, and plays a critical role in controlling the cytosolic Ca2+ level of eukaryotic cells. The N-terminal region of IP3R is responsible for binding to IP3 and Ca2+ binding proteins such as calcium-binding protein 1 (CaBP1) and calmodulin (CaM). We presented crystal structures of the N-terminal region (NT) of IP3R1 with (3.6 Å) and without (3.0 Å) IP3 bound. Another ligand, cytosolic Ca2+ can both activate and inhibit IP3R channel activity. As the Ca2+ concentration increases, the channel is activated, but high concentration of Ca2+ inhibited channel activity. Although the exact regulatory mechanism of the IP3R by Ca2+ is unknown, the effects of Ca2+ on IP3R might also be mediated by accessory proteins, such as CaM and CaBPs. In order to understand the regulatory mechanism of IP3R1 by CaBP1, NMR spectroscopy was employed. We used the chemical shift perturbation (CSP) and paramagnetic relaxation enhancement (PRE) data to dock the structure of CaBP1 C-lobe onto the structure of IP3R1-NT. In addition, conformational dynamics of N-terminal regions of IP3R1 and IP3R3 upon IP3 binding were analyzed by hydrogen/deuterium exchange mass spectrometry (HDX-MS). The deuterium uptake levels of amide hydrogens between apo-states and IP3-bound states of IP3Rs were compared.

Keyword: IP3 receptor (IP3R), protein structure, X-ray crystallography, Nuclear Magnetic Resonance (NMR), hydrogen/deuterium exchange mass spectrometry (HDX-MS)

***Funding Source*:** This work was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (2012R1A1A1039738; 2014R1A1A2054691).

Disclosure Statement: None of the authors have any conflicts of financial interest to declare.