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Structural Insights into the Gating and Regulation of IP3R Channels

The inositol 1,4,5-trisphosphate receptors (IP3Rs) are a family of Ca2+ release channels localized predominately in the endoplasmic reticulum of all cell types. They function to release Ca2+ into the cytoplasm in response to binding of IP3 produced by diverse cellular stimuli, generating complex Ca2+ signals that regulate numerous cell physiological processes ranging from gene transcription to secretion to learning and memory. However, the molecular mechanism of how the receptor senses and decodes ligand-binding signals into gating motion remains unknown. In attempt to elucidate the molecular mechanism of the channel gating and its regulation, we solved the electron cryo-microscopy structure of IP3R from rat cerebellum to 4 Å resolution in the presence of activating ligands. Comparison with the IP3R structure in the Apo-state reveals striking ligand-induced conformational rearrangements within cytoplasmic domains coupled to the dilation of a hydrophobic constriction at the gate. Our studies provide critical insights into the mechanistic principles by which ligand-binding allosterically gates IP3R channel.

Keck Seminar

Friday, March 8, 4pm

BioScience Research Collaborative

Room 280 (2nd Floor)

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