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Cryo-EM Analysis of IP3R channel in a Lipid Bilayer

Dr. Baker received her Ph.D. from Baylor College of Medicine in the Structural and Computational Biology and Molecular Biophysics graduate program. Her early research work on voltage- and ligand-gated ion channels and their molecular regulation shaped her perspective on the importance of elucidating protein structures to inform and interpret biochemical studies. Since then, she has focused on the structural analysis of membrane proteins using single-particle electron cryo-microscopy and computational modeling. During her postdoctoral work at the National Center for Macromolecular Imaging she was a co-developer of a computational approach for de novo atomic modeling from EM density maps using a novel implementation of the traveling salesman algorithm. In 2012, she joined Irina Serysheva's lab as a senior postdoc in the Department of Biochemistry and Molecular Biology at UTHealth McGovern Medical School and played a key role in analyzing the first near-atomic resolution structure of the full-length, tetrameric Ca2+ release channel, IP3R, by single-particle cryo-EM. Dr. Baker is currently an Assistant Professor at UTHealth and a Cryo-EM specialist for the UTHealth Cryo-EM Core. Her current research is committed to answering key questions regarding how ion channels process complex regulatory signals, and how these signals affect channel structure and function.

Abstract: Inositol 1,4,5-trisphosphate receptors (IP3Rs) are tetrameric intracellular cation channels ubiquitously expressed in mammalian cells and located predominantly in the endoplasmic reticulum (ER) membranes. IP3Rs mediate Ca2+ release from the ER into the cytosol and thereby involved in many physiological processes. IP3R structures in closed and ligand-bound states have been captured by single-particle cryo-EM under conditions in which channel protein was solubilized with detergent. However, ion channels reside in biological membranes, where lipids have important structural and regulatory roles. Here, we present the structure of full-length neuronal type IP3R reconstituted in lipid nanodisc determined by single-particle electron cryo-microscopy. The lipid-bound structure shows improved features that enabled us to build an atomistic model of IP3R1 including regions that were not previously resolved. Our study suggest conserved locations of protein-integrated lipids among homotetrameric ion channels that is critical for their structural and functional integrity despite the diversity of structural mechanisms for their gating.

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