Structure & Dynamics of Viral and Bacterial Ion Channels and Transporters

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Enveloped viruses and bacteria encode membrane-bound ion channels and transporters that are important for the survival of these pathogens. Elucidating the structure, dynamics and mechanism of action of these membrane proteins is crucial for advancing our fundamental knowledge of channels and transporters in general and for designing antiviral and antibiotic drugs. In this seminar I will present my laboratory's recent studies of the structures and dynamics of the influenza B M2 proton channel [1], the SARS-CoV-2 E cation channel [2], and the bacterial transporter EmrE [3]. Using multidimensional correlation ^{13}C and ^{15}N NMR and ^{19}F NMR for long-range distance measurements, we have determined the atomic structures of these three membrane proteins in lipid bilayers. For BM2, our data revealed conformational changes between the closed and open states that explain the proton conduction direction of BM2. ^{13}C-detected water proton relaxation data and recoupled chemical shift anisotropies revealed that water in the closed and open BM2 channels have distinct dynamics and orientations [4]. These results give insights into how water mediates proton hopping to the proton-selective histidine of the protein. The structure of the SARS-CoV-2 E protein indicates a tight hydrophobic channel stabilized by an aromatic gate. Chemical shift perturbations indicate that the N-terminus of the channel is the binding site for two inhibitors, hexamethylene amiloride and amantadine. We determined the structure of EmrE bound to a substrate, tetraphenylphosphonium, using ^{1}H-detected 3D NMR experiments and ^{1}H-^{19}F distance measurements between the protein amide protons and the fluorinated substrate. By changing the pH and hence the protonation state of the protein, we found that the substrate-binding structure changes significantly. These results give unprecedented insights into the alternating-access mechanism and the proton dependence of membrane transport by EmrE.

References

[1] V.S. Mandala, A.R. Loftis, A.A. Shcherbakov, B.L. Pentelute, M. Hong, Atomic Structures of Closed and Open Influenza B M2 Proton Channel Reveal the Conduction Mechanism, Nat. Struc. Mol. Biol., 27 160-167 (2020).
[2] V.S. Mandala, M.J. McKay, A.A. Shcherbakov, A.J. Dregni, A. Kolocouris, M. Hong, Structure and drug binding of the SARS-CoV-2 envelope protein transmembrane domain in lipid bilayers, Nat. Struct. Mol. Biol., 27 1202-1208 (2020).
[3] A.A. Shcherbakov, G. Hisao, V.S. Mandala, N.E. Thomas, M. Soltani, E.A. Salter, J.H. Davis, Jr., K.A. Henzler-Wildman, M. Hong, Structure and dynamics of the drug-bound bacterial transporter EmrE in lipid bilayers, Nat. Commun., 12 172 (2021).
[4] M.D. Gelenter, V.S. Mandala, M.J.M. Niesen, D.A. Sharon, A.J. Dregni, A.P. Willard, M. Hong, Water orientation and dynamics in the closed and open influenza B virus M2 proton channels, Commun. Biol., 4 338 (2021).

Biosketch of Mei Hong

Prof. Mei Hong obtained her BA degree in chemistry with *summa cum laude* from Mount Holyoke College in 1992, and her PhD from the University of California, Berkeley in 1996 (in Alex Pines' lab). After a one-year postdoctoral stint at MIT in Bob Griffin's lab, she began her independent career at the University of Massachusetts, Amherst before moving to Iowa State University in 1999. She became a full professor in 2005, held the first John D. Corbett Professorship in 2007-2010, and returned to MIT as a full professor in 2014. She has received numerous awards for her creative development and application of multidimensional and multinuclear solid-state NMR methods to elucidate the structure, dynamics and mechanism of action of biological systems, including membrane proteins, amyloid proteins, and plant cell walls.