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Timothy A Cross

Florida State University, USA

Membrane protein structure, dynamics & function: Oriented sample and magic angle sample spinning solid state NMR

Statement of the Problem: Unlike water soluble proteins that have a relatively homogeneous environment, membrane proteins exist in a dramatically heterogeneous environment. The result is protein structure that is stabilized by a different balance of molecular interactions for the membrane embedded portion of the protein compared to the water soluble or membrane interfacial regions of the protein. The result is there is a need to model the membrane environment as closely as possible to that of the native environment for structural, dynamic and functional characterizations.

Methodology: Biological solid-state NMR provides a unique opportunity to model the membrane environment with liquid crystalline lipid bilayers and a wide variety of lipids. The samples can be prepared either as liposomes for magic angle sample spinning or as uniformly oriented samples for the spectroscopy. The former provides solution like spectra for both distance and isotropic chemical shift restraints, while oriented samples provide absolute restraints that restrain the atomic sites in the protein structure to the bilayer normal. In addition to structural restraints it is possible to characterize the protein's dynamics and kinetic rates.

Findings, Conclusion & Significance: The structure, dynamics and kinetics associated with the M2 proton channel from influenza A have been characterized yielding a unique mechanism for proton transport by this important drug target. In addition, the cholesterol binding to M2 has been found to stabilize the amphipathic helix in the lipid interface is an essential feature for this protein's functional role in viral budding. Recent structural studies of the CrgA protein from *Mycobacterium tuberculosis* have characterized a dimeric structure stabilized primarily by intermolecular β-sheet in the membrane interfacial region. The protein is part of the cell division apparatus and appears to play a role in recruiting multiple proteins to the divisome, potentially through its trans-membrane domain.

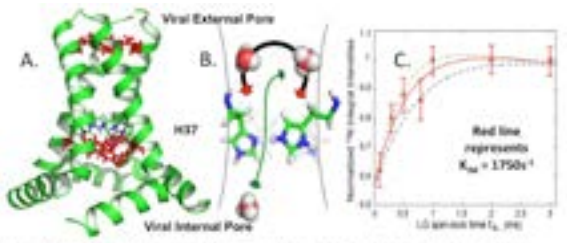

Figure 1: The M2 proton channel. A) Structure derived from NMR Orientational & Distance Restraints highlighting in red the proton gates and the His37 proton transfer residues. B) An illustration of the futile and conductance cycles for proton translocation. C) Measurement by NMR of the specific exchange rate between water protons and His37 protons.

Biography

Timothy A Cross has more than 30 years of experience in characterizing membrane proteins in lipid bilayer environments using solid state NMR, of liquid crystalline bilayer preparations of peptides and proteins. This has brought light to a fundamental understanding of membrane protein biophysics, that has led to detailed functional characterizations of membrane channels, the gramicidin mono-valent cation channel and the influenza A M2 proton channel. In both systems, the unique features of the membrane environment play crucial roles in the functional mechanisms and kinetics of ion conductance. This, understanding of the influence of membrane and lipid environments using solid state NMR has driven his research at the frontier of membrane protein biophysics.

cross@magnet.fsu.edu