

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Sequence to Topography Relationship in Membrane Inserted Hydrophobic Helices

By

Shyam S. Krishnakumar

Hydrophobic α -helices have been widely used to study membrane protein sequence-structure relationship in model membranes. Our lab has developed fluorescence methods to determine the topography of membrane-inserted hydrophobic helices, and to understand the equilibria describing the topographic stability. Using this system, I addressed the following questions: (A) Minimum Length Threshold for Stable TM Topography: My work showed that a 13 residue hydrophobic sequence was sufficient to form a stable TM structure in physiologically relevant bilayer widths and the ability of these short hydrophobic sequences to form TM helices in the presence of substantial negative mismatch (10 Å) implied that lipid bilayers have a considerable ability to adjust to hydrophobic mismatch. (B) Helix Shifting Potential of Hydrophilic Residues: I found that hydrophilic residues at some positions within hydrophobic helices have a tendency to 'shift' the transverse position of transmembrane (TM) helices within lipid bilayers, such that the polar residue locates closer to the surface of the bilayer, shortening the effective TM length. The extent of shift depends on the identity of the hydrophilic residue and the shift is controlled by the combination of amino acid hydrophilicity and the ability of their side chains to position polar groups near the bilayer surface (snorkeling). (C) Functional Relevance of Transverse Shifts in TM Helix: I investigated the structural consequences of a pathogenic hydrophilic mutation in the TM domain of ErbB2 receptor. My results showed that the hydrophilic mutation in the TM domain induces a shift in TM helix position and thus redefines the transmembrane boundary. This indicates a new mode of receptor deregulation in ErbB2 receptor, linked to disease-related changes. 4) Characterizing the Membrane Topography of Poliovirus Proteins 3A and 3AB (In collaboration with Dr. Eckard Wimmer, Microbiology Dept) Fluorescence studies showed that the hydrophobic domain forms a stable TM structure in mature 3A protein, but adopts a non-TM surface topography in context of the precursor 3AB protein. The hydrophobic sequence could insert in TM form, only when the C-termini 3B domain was removed. Further, we identified that shortened C-terminal part of the putative hydrophobic segment (16 residues rather than 22 residues) spans the lipid bilayer.

Date: 10/04/2007

Time: 1.30 PM

Place: Life Sciences Building, Room 038

Program: Biochemistry and Structural Biology

Dissertation Advisor: Dr. Erwin London