Proteins on the Edge (of the Lipid Bilayer)

Melanie Cocco, Ph.D.
Department of Molecular Biology and Biochemistry
Department of Pharmaceutical Sciences
University of California, Irvine

Date: 10/27/17
Time: 3:00 PM
Location: COB 267
For more information contact: Andy LiWang; aliwang@ucmerced.edu

ABSTRACT

Structural studies of proteins peripherally associated with cell membranes are difficult because the environment consists of both aqueous and lipid phases. In some cases, detergent micelles and detergent/lipid bicelles can mimic the anisotropy of cell membranes and provide an environment suitable to fold a membrane-associated protein. Here I will present a strategy to determine peripherally associated membrane protein structures including the structural studies on the neuronal growth inhibitor described below.

Compelling evidence indicates that repair of damage to the central nervous system (CNS) is inhibited by the presence of protein factors within myelin that prevent axonal regrowth. Myelin growth inhibitors and their common receptor have been identified as targets in the treatment of spinal cord injury and stroke. We have recently determined the NMR structure of one of the myelin growth inhibitors, the neurite outgrowth inhibitor (Nogo). We studied the structure of this protein alone and in the presence of dodecylphosphocholine micelles to mimic the natural cell membrane environment. Using several paramagnetic probes, we have defined portions of the growth inhibitor that are accessible to solvent (and consequently the Nogo receptor). Mutagenesis probed through phage-display confirms that the positions predicted to be extra-cellular are sensitive to receptor binding. Using computational docking methods, NMR data and mutagenesis results, we calculated the optimal protein-protein interface between our structure of Nogo and the Nogo receptor. With these data we predict that residues (28-58) are available to bind the Nogo receptor which is entirely consistent with functional assays. Moreover, the conformations and relative positions of side chains recognized by the receptor are now defined and may be useful in antagonist design.

In addition, I will highlight our recent work in developing vaccines based on membrane protein formulations.

BIO:

Melanie Cocco received her BS in Chemistry from Virginia Tech where she did her undergraduate research in synthetic organic chemistry. She then went to Penn State to study protein NMR spectroscopy (PhD in Chemistry). She was awarded an NIH postdoctoral fellowship to perform studies in Molecular Biophysics and Biochemistry at Yale. There she worked on membrane protein biophysics using NMR spectroscopy. She was then hired as an Assistant Professor in the Department of Molecular Biology and Biochemistry at UC Irvine in 2003 and promoted to Associate Professor in 2010. She established a research laboratory with emphasis on defining membrane protein structures and DNA binding protein dynamics using NMR spectroscopy. Applications of this work include the treatment of CNS damage, understanding cancer biology and vaccine development.