Abstract for an Invited Paper
for the MAR12 Meeting of
The American Physical Society

High-resolution Structures of Protein-Membrane Complexes by Neutron Reflection and MD Simulation: Membrane Association of the PTEN Tumor Suppressor

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The lipid matrix of biomembranes is an in-plane fluid, thermally and compositionally disordered leaflet of 5 nm thickness and notoriously difficult to characterize in structural terms. Yet, biomembranes are ubiquitous in the cell, and membrane-bound proteins are implicated in a variety of signaling pathways and intra-cellular transport. We developed methodology to study proteins associated with model membranes using neutron reflection measurements and showed recently that this approach can resolve the penetration depth and orientation of membrane proteins with Ångstrom resolution if their crystal or NMR structure is known. Here we apply this technology to determine the membrane bindung and unravel functional details of the PTEN phosphatase, a key player in the PI3K apoptosis pathway. PTEN is an important regulatory protein and tumor suppressor that performs its phosphatase activity as an interfacial enzyme at the plasma membrane-cytoplasm boundary. Acting as an antagonist to phosphoinositide-3-kinase (PI3K) in cell signaling, it is deleted in many human cancers. Despite its importance in regulating the levels of the phosphoinositoltriphosphate PI(3,4,5)P_3, there is little understanding of how PTEN binds to membranes, is activated and then acts as a phosphatase. We investigated the structure and function of PTEN by studying its membrane affinity and localization on in-plane fluid, thermally disordered synthetic membrane models. The membrane association of the protein depends strongly on membrane composition, where phosphatidylserine (PS) and phosphatidylinositol diphosphate (PI(4,5)P_2) act synergetically in attracting the enzyme to the membrane surface. Membrane affinities depend strongly on membrane fluidity, which suggests multiple binding sites on the protein for PI(4,5)P_2. Neutron reflection measurements show that the PTEN phosphatase "scoots" along the membrane surface (penetration < 5 Å) but binds the membrane tightly with its two major domains, the C2 and phosphatase domains. In the bound state, PTEN's regulatory C-terminal tail is displaced from the membrane and organized on the far side of the protein, ~ 60 Å away from the bilayer surface, in a rather compact structure. The combination of binding studies and neutron reflection allows us to distinguish between PTEN mutant proteins and ultimately may identify the structural features required for membrane binding and activation of PTEN. Molecular dynamics simulations, currently in progress, refine this structural picture further.