Center for Theoretical Biological Physics

SEMINAR

"pH-dependent Transmembrane Peptide Insertion: Mechanism and Uses in Tumor Targeting and Drug Delivery"

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Abstract: The discovery that the C helix of Bacteriorhodopsin exhibits spontaneous, pH-dependent insertion to form a helix across lipid bilayers has led to the use of related peptides, pHLIPs (pH (Low) Insertion Peptides), to study peptide insertion across bilayers, to selectively target cargoes to tumors and other acidic tissues in vivo, and to deliver molecules across the plasma membranes of living cells. A pHLIP has three kinds of monomeric states: soluble in water as a largely unstructured peptide, bound to the surface of a membrane as a largely unstructured peptide, and inserted as an alpha helix with its C-terminus across the membrane. At physiological pH, the equilibrium is toward water and the membrane surface, which explains its lower affinity for cells in healthy tissue; at acidic pH, titration of carboxyl groups shifts the equilibrium toward membrane insertion and tissue accumulation. Because pHLIP is unfolded on the surface of a bilayer and folding is pH-triggered, we are able to begin to observe and understand the molecular events that accompany the insertion and folding of a peptide entering a bilayer. When the pH is dropped, it is found that a helix forms rapidly on the bilayer surface, followed by a slow insertion across it in several kinetically distinct steps. The exit pathway when the pH is suddenly raised is more rapid, and includes partial unfolding of the helix while still in the bilayer. Lipid composition and sequence features affect the insertion pK and pathway intermediates. pHLIPs target acidic tissues *in vivo*, where the transmembrane insertion stabilizes them in cells. We have shown targeting of dyes, radioisotopes and nanogold to tumors in mice, and have studied the parameters of molecules that can be delivered into cells.