When peptide meets lipid: greasy folding
Thermodynamics of lipid-protein interaction

Joachim Seelig
Biozentrum of the University of Basel

This review is focused on peptide molecules which exhibit a limited solubility in the aqueous phase and bind to the lipid membrane from the aqueous medium. Surface adsorption, membrane insertion, and specific binding are usually accompanied by changes in the heat content of the system and can be measured conveniently with isothermal titration calorimetry, avoiding the necessity of peptide labeling. The driving forces for peptide adsorption and binding are hydrophobicity, electrostatics, and hydrogen bonding. An exclusively hydrophobic interaction is exemplified by the immunosuppressant drug cyclosporine A. Its insertion into the membrane can be described by a simple partition equilibrium $X_b = K_0 C_{eq}$.

If peptide and membrane are both charged, electrostatic interactions are dominant leading to non-linear binding curves. The concentration of the peptide near the membrane interface can then be much larger than its bulk concentration. Electrostatic effects must be accounted for by means of the Gouy-Chapman theory before conventional binding models can be applied.

A small number of peptides and proteins bind with very high affinity to a specific lipid species only. This is illustrated for the lantibiotic cinnamycin (Ro 09-0198) which forms a 1:1 complex with phosphatidyethanolamine with a binding constant of 10^8 M^{-1}.

Protein folding is a problem of central importance in biophysics and molecular biology. Many proteins fold reliably and quickly to their native state despite the astronomically large number of possible conformational intermediate states (Levinthal's paradox). A statistical search of the whole conformational space would take an infinitely long time and is unlikely. Additional kinetic and energetic constraints must direct protein folding. One possible energy constraint is the interaction with the lipid membrane. Many amphipathic peptides such as the bee venom melittin, antibacterial peptides, or lipoproteins interact with the lipid membrane to form an α-helix. Using isothermal titration calorimetry (ITC) and D,D-substituted peptides it is possible to provide a complete thermodynamic description of the membrane-induced random-coil $\rightleftarrows$ α-helix transition and to compare it with the same process in isotropic aqueous solution.

A second structural element of proteins is the β-structure. A particularly relevant example of β-structure formation are Alzheimer peptides which are random coil in dilute solution but aggregate to β-structured fibrils at higher peptide concentrations. The random-coil $\rightleftarrows$ β-structured aggregate transition appears to be a 2-state equilibrium which can be shifted towards β-structure formation upon addition of negatively charged lipids. It can be investigated quantitatively with circular dichroism spectroscopy and ITC and explained in terms of an electrostatic attraction/surface partition model.