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When peptide meets lipid: greasy folding

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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 \rightleftharpoons 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 \rightleftharpoons 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.