

**PEPTIDE-LIPID INTERACTIONS IN A BILAYER: MOLECULAR MODELLING STUDIES**

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Membrane proteins are essential constituents of the biological membranes. The lipid component of biomembranes, in the form of a bilayer, provides the basic physical barrier, whilst the membrane proteins regulate the permeability of this barrier to specific components and provide the membranous biological functions. Membrane proteins can be classified into two broad categories, integral and peripheral. Most biomembranes contain both types of membrane proteins. Integral membrane proteins have at least one segment that is embedded in the phospholipid bilayer. Transmembrane proteins span the entire phospholipid bilayer. The bilayer has two distinct regions, a polar interface and non-polar core. An integral protein contains mainly residues with hydrophobic side chains that interact with hydrocarbon chains of phospholipids in the membrane core but also residues with hydrophilic side chains that interact with polar headgroups of phospholipids at the membrane interface. These interactions anchor the protein to the membrane. The membrane-spanning domains are  $\alpha$  helices or multiple  $\beta$  strands. Peripheral membrane proteins are entirely outside of the membrane, but are bound to it by weak molecular attractions.

To elucidate the details of the protein-membrane interactions we adopted a strategy that involves studying the basic interactions of small peptides (~25 amino acids) with lipids in a bilayer of a lipid composition representative for the animal cell membrane. The study was carried out using molecular modelling methodology. We have chosen two computer models; one stands for the integral, the other for the peripheral membrane protein. In both systems, the animal cell membrane was modeled by a palmitoyl-oleoyl-phosphatidylcholine-cholesterol (POPC-Chol) bilayer. In the first model, the membrane spanning helical fragment of EGF receptor (EGF peptide) was inserted vertically to the bilayer surface, in the second, magainin-2 amide (M2a) was located on the bilayer surface [Murzyn, K. *et al.* **Lect. Notes Comput. Sc.** 3037 (2004) 325]. EGF receptor is a constitutive membrane protein, its transmembrane fragment consists mainly of hydrophobic amino acids. M2a is a natural cationic peptide expressed in the skin of a frog *Xenopus leavis* that selectively kills bacteria at concentrations that are harmless to animal cells. M2a consists of non-polar and charged (four positively charged Lys, N-terminus, and one negatively charged Glu) residues. In the membrane, M2a forms an  $\alpha$ -helix of a distinct hydrophobic moment, i.e., the helix possesses a polar and non-polar face [Gesell, J. *et al.* **J.**

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**Biomol. NMR** 2 (1997) 127]. Molecular dynamics (MD) simulations of the two systems were carried out for 20 ns. During simulations, the peptides retained their helical structure.

Analysing basic interactions between the peptides and membrane lipids, formations of intermolecular hydrogen (H-) bonds, charge pairs, water bridges and van der Waals (vdW) contacts, were examined using geometrical criteria [Murzyn, K. *et al. Biophys. J.* 81 (2001) 170]. The EGF peptide, which has only one polar residue in its sequence (ARG) practically does not interact specifically with POPC or Chol. M2a, instead, interacts specifically with POPC and Chol. M2a is linked directly to POPC by H-bonds and charge pairs and indirectly via water bridges. Furthermore, M2a forms direct H-bonds with Chol, which distorts its helical structure. Non-polar residues of both peptides interact with hydrocarbon chains of POPC and Chol via vdW interactions. VdW interactions between EGF peptide and lipids are tighter than between M2a and lipids. This result is consistent with our intuition, which suggests that peripheral proteins are bound to the membrane mainly via polar interactions, whereas, non-polar interactions should dominate in the case of integral proteins.