The distribution of amino acids for membrane proteins within a model of bilayer

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The currently known structures of membrane proteins are very few. Their relationship with the bilayer during folding and membrane insertion is obscure and consequently so is the orientation of membrane proteins within membranes. A program called IMPALA is used in our lab to test the orientation of peptides in a theoretical model of bilayer. Recently, a panel of 20 X-Ray structures of transmembrane proteins were analyzed against this model (Basyn et al., 2001). It appears that membrane thickness varies and it is very different depending on organism's cellular type. Consequently, a hydrophobic mismatch can strongly affect protein and lipid organization. Therefore, we studied the insertion of X-ray structures within a bilayer model of variable thickness to find the optimal thickness for each membrane protein (Basyn et al., 2003). This approach allows for the protein structures to be kept constant and at each membrane thickness, the protein is tilted and rotated to fit in the best possible way. The conditions are said to be optimal when the insertion energy is minimal.

Finally, we studied the amino acids composition required for each protein at optimal thickness using "Pex-Files", a new technique developed in our lab. We analyzed the distribution of amino acids in the water, interface and acyl chain layers of the membrane and compared our results with the literature. Analyses of the structure of transmembrane proteins suggest that two types of amino acids may be of particular importance for interactions of membrane proteins with the interfacial region. First, aromatic amino acids, in particular tryptophans, which are enriched at both ends of transmembrane fragments and appear to have a preference for interaction with the interface. Second, charged residues, which are also primarily located near the membrane interfaces. Positively charged residues interact with negatively charged phospholipids and are predominantly positioned on the cytoplasmic side, according to the positive inside rule of Von Heijne (1992). Statistical analysis of amino acid distribution shows that many hydrophobic residues and a few hydrophilic ones are accessible. Aromatic residues, at least tyrosine and tryptophan, make up the "aromatic belt" described in the literature (Ulmschneider and Sansom, 2001), whereas phenylalanine is globally distributed throughout the whole bilayer. Glycine occurs more frequently in membranous β structures than in soluble proteins. The distribution of charged residues of α protein, except glutamic acid, correlate with the positive-inside rule which held that cytoplasmic segments are more positively charged.

Our data suggest that most X-ray structures insert in membranes as described in experimental data. The statistics for amino acid distribution within the bilayer model could help to reveal the significance of each type of amino acid within the bilayer and thus help to improve our understanding of the folding of membrane proteins within a cellular membrane.