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The importance of the membrane interface as the reference state for membrane protein stability

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Abstract

The insertion of nascent polypeptide chains into lipid bilayer membranes and the stability of membrane proteins crucially depend on the equilibrium partitioning of polypeptides. For this, the transfer of full sequences of amino-acid residues into the bilayer, rather than individual amino acids, must be understood. Earlier studies have revealed that the most likely reference state for partitioning very hydrophobic sequences is the membrane interface. We have used μs-scale simulations to calculate the interface-to-transmembrane partitioning free energies $\Delta G_{S\rightarrow TM}$ for two hydrophobic carrier sequences in order to estimate the insertion free energy for all 20 amino acid residues when bonded to the center of a partitioning hydrophobic peptide. Our results show that prior single-residue scales likely overestimate the partitioning free energies of polypeptides. The correlation of $\Delta G_{S\rightarrow TM}$ with experimental full-peptide translocon insertion data is high, suggesting an important role for the membrane interface in translocon-based insertion. The choice of carrier sequence greatly modulates the contribution of each single-residue mutation to the overall partitioning free energy. Our results demonstrate the importance of quantifying the observed full-peptide partitioning equilibrium, which is between membrane interface and transmembrane inserted, rather than combining individual water-to-membrane amino acid transfer free energies.

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