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Membrane Protein Folding: Biology Meets Thermodynamics

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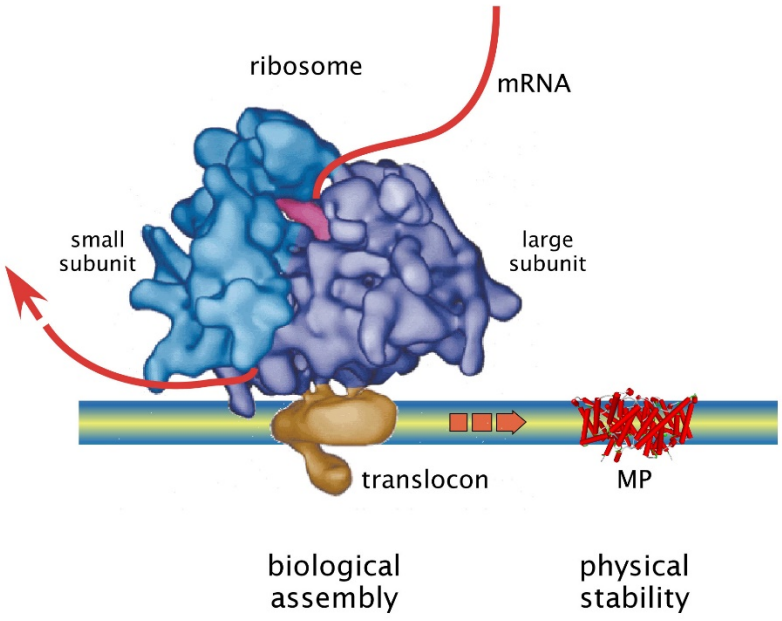
The prediction of the 3D structures of membrane proteins (MPs) from sequence is a daunting challenge despite the topological constraints imposed by the membrane lipid bilayer. All available evidence indicates that membrane proteins are equilibrium structures, which means that structure should be predictable from sequence if the physicochemical forces driving folding were completely understood. So far, our understanding of the interactions that shape structure are far from complete. Because the *in vivo* folding of membrane proteins, guided by co-transitional insertion via the SecY/Sec61 translocon complexes, must ultimately be determined by the physicochemical rules of MP stability, we are studying the relationship between spontaneous transmembrane (TM) helix insertion and translocon-guided TM helix insertion. We are doing this by means of equilibrium molecular dynamics simulations of TM helix insertion[1] and *in vitro* measurements of Sec61-guided insertion of TM helices into dog pancreas microsomes[2]. The insertion free energies determined in the two types of experiments are remarkably similar. We find that the lipid bilayer interface plays a crucial role in spontaneous folding and insertion of TM helices, suggesting that the bilayer interface also plays a crucial role in translocon-guided insertion[3]. The traditional model of translocon-guided insertion posits that the nascent chain emerging from the ribosome passes through the translocon and moves into the bilayer through the so-called lateral gate of the translocon. Our work suggests an alternate view of translocon-guided TM helix insertion[4].



References

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