Mechanisms of protein insertion by the SRP and GET systems

More than 25% of the cellular proteome comprise membrane proteins that have to be inserted into the correct target membrane. Most membrane proteins are delivered to the membrane by the signal recognition particle (SRP) pathway which relies on the recognition of an N-terminal signal sequence. This co-translational mechanism elegantly couples synthesis with insertion and helps to minimize problems due to the hydrophobic nature of the cargo proteins. In contrast, tail-anchored (TA) membrane proteins carry their targeting signal within their single C-terminal transmembrane region. They utilize a post-translational mechanism for membrane insertion - the recently discovered GET pathway (guided entry of tail-anchored membrane proteins). The SRP and GET pathways are regulated by GTP and ATP binding proteins of the SIMIBI family, respectively. A comparative analysis of these two pathways allows to unravel mechanistic details and common principles of regulation. Recent insights into the activation mechanism of SRP GTPases and the ATPase cycle of Get3, the central player in the GET pathway will be highlighted.