

4.2: Insertion of Membrane Proteins into Lipid Membranes

Integral membrane proteins are ubiquitous throughout living organisms, ranging from prokaryotes to mammals, accounting for approximately 20-30% of all proteins. (Wallin et al. 1998) They perform a diverse set of functions ranging from signal transduction, to ion transport or even photosynthetic reaction centers. While their activity might vary dramatically, all these proteins experience a similar challenge. They must traverse the amphiphilic lipid membrane to reach their correctly folded state. The ways in which nature has overcome this challenge will be the primary focus of this page.

Features and diversity of membrane proteins

Prior to discussing the mechanisms of membrane insertion, it is important to characterize key features of transmembrane proteins and their topology.

Characteristics of transmembrane domains

A transmembrane domain (TMD) is defined as a region of a polypeptide chain that completely traverses the hydrophobic region of the bilayer. The most common TMD's are 20 amino acids long and for a tightly coiled structure known as an α -helix. An α -helix is the preferred structure as it maximizes hydrogen bonding within the backbone of the chain, effectively shielding the hydrophilic regions of the amino acid backbone from the surrounding acyl chains of the lipids. An integral membrane protein (IMP) is composed of one or more TMD's. When studying an integral membrane protein's sequence, it is possible to identify the TMDs by generating a hydrophobicity plot. The TMDs will correspond to regions of amino acids that are hydrophobic (Kyte & Doolittle 1982). The determination of TMDs through this method are not always accurate as the insertion is heavily influenced by both the proximal and distal amino acids. In Figure 4.2.1, a hydrophobicity plot of a G-coupled receptor is shown to have polar amino acids in their transmembrane domains.

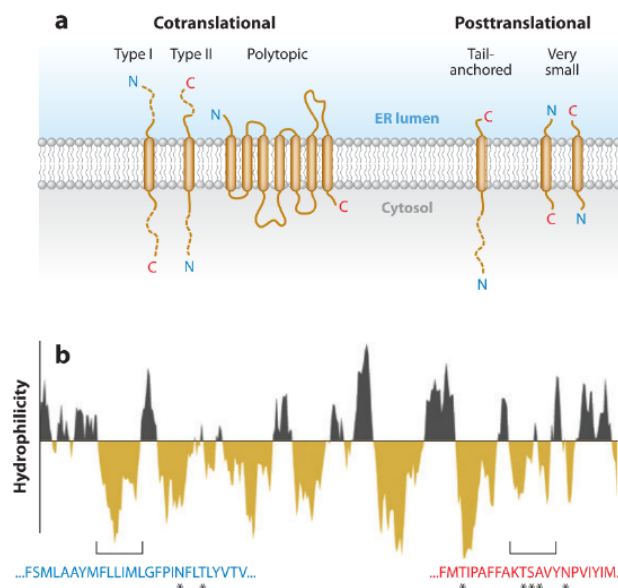


Figure 4.2.1: Structural diversity of membrane proteins (Shao & Hegde 2011)

Determinants of topology

The topology of an IMP refers to the orientation of the protein in the membrane. A protein can be in either the type I or type II topologies. Type I indicates that the N-terminus of the protein passes through the membrane first. Type II topology implies that the N-terminus does not cross the membrane, causing the later segments of the protein to pass through first instead. The driving force to choose one conformation over another is composed of several additive features of the protein. The most prominent effect, at least for bacteria, comes from the positive inside rule. The positive inside rule states that positively charged amino acids, such as arginine and lysine, will not cross the membrane and remain in the cytosol (Hatmann et al. 1989). This is dictated by the strong positive charges interacting repulsively with the channel that I will describe later in this page. In bacteria the asymmetry between the leaflets and the strong proton motive force across the membrane cause the cytosolic side of the membrane to be far more favorable for positive amino acids compared to the periplasmic side. (van Klompenburg 1997)

Cotranslational membrane protein insertion

The pathway for the insertion of membrane proteins has been highly conserved across organisms and has two distinct steps: recognition and targeting of a nascent IMP and then its insertion into the membrane.

Recognition and Targeting

Recognition occurs on the ribosome as the nascent polypeptide chain emerges from the exit channel by the **Signal Recognition Particle (SRP)**. This protein has a nonspecific hydrophobic channel that interacts with amino acids that would form a transmembrane domain based on the presence of numerous hydrophobic residues. Upon binding, translation is arrested and the SRP-ribosome complex searches for the eukaryotic SRP Receptor (SR) or bacterial FtsY. Once the ribosome-SRP-receptor complex is formed bound it diffuses through the membrane until it interacts with the Sec translocon. The nascent chain is then transferred to the channel. The critical aspect of this process is that it prohibits the hydrophobic region of the polypeptide from exposure to the hydrophilic cytosol to avoid misfolding and aggregation (Grudnik et al. 2009).

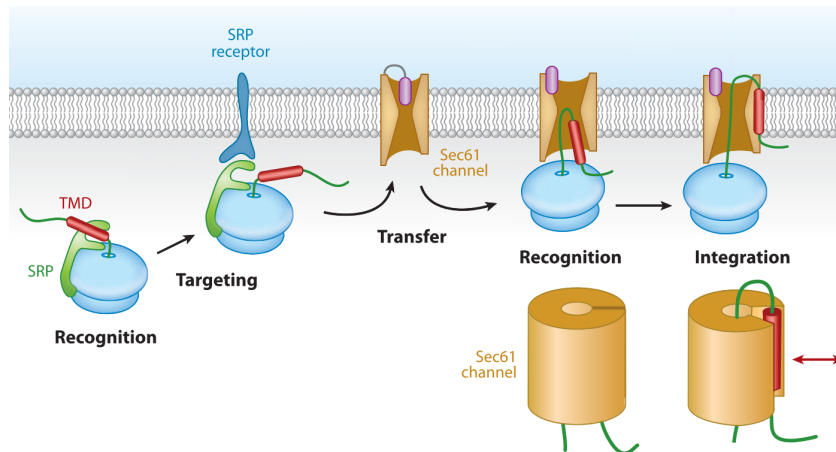


Figure 4.2.2: General steps of cotranslational membrane protein insertion. (Shao & Hegde 2011)

Sec translocon

In both prokaryotes and eukaryotes, there are protein conductive channels generally referred to as Sec translocases. These channels have two fundamental functions that enable the insertion of proteins into the membrane. They contain a hydrophilic channel that allows hydrophilic residues of a polypeptide to pass through the membrane as well as a lateral gate that opens to expose the interior of the channel to the lipid acyl chains. This allows for hydrophobic residues to enter through the channel and then interact directly with the lipid tails while avoiding the polar head groups. These channels therefore allow the nascent chain that is being translated to effectively “thread” in and out of the membrane as many times as is required to reach the final structure. (van den Berg et al. 2004).

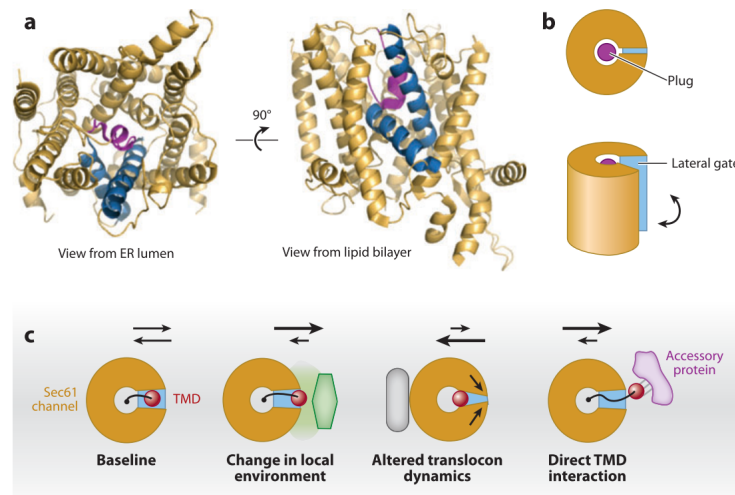


Figure 4.2.3: The Sec61 translocon and potential accessory factors. (Shao & Hegde 2011)

Accessory factors

While the translocase complex is the primary requirement for most membrane proteins, more complex IMPs require accessory factors to aid in its insertion and maturation. Below is a breakdown of different accessory factors for prokaryotes and eukaryotes.

Eukaryotes

Numerous other membrane proteins have been found to interact with the Sec translocon complex in eukaryotes, however their necessity remains unclear. Enzymes like the signal peptidase and the oligosaccharyl transferase have been found to aid in the folding and maturation of certain IMPs by either cleaving or glycosylating respectively (Yamagishi et al. 2011). The translocon-associated protein (TRAP) complex may help fortify the ribosome-translocon complex. The translocating-chain associating membrane (TRAM) protein is currently expected to insert TMDs with weak hydrophobicity and therefore is only required for certain IMPs. (Heinrich et al. 2000)

Prokaryotes

As in eukaryotes, there are several accessory factors that have been found to aid in the insertion of IMPs in prokaryotes. SecA is an ATPase that has been shown to be essential to push highly hydrophilic proteins through the Sec channel (Zimmer et al. 2008). The YidC insertase has been shown to aid in the lateral partitioning of IMPs out of the channel into the membrane. Its role is expected to be that of a foldase which helps with the formation of α -helices (Beck et al. 2001). It has also been found that the presence of the phospholipid phosphatidylethanolamine (PE) is required for the folding of certain IMPs. As PE is a positively charged lipid, it interacts with acidic residues that flank the TM and stop the residues from wanting to translocate to the positively charged periplasmic side of the membrane (Bogdanov et al. 2008).

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