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# Protein translocation across the inner membrane of Gram-negative bacteria: the Sec and Tat dependent protein transport pathways

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**Abstract**

Gram negative bacteria possess a large variety of protein transport systems, by which proteins that are synthesised in the cytosol are exported to destinations in the cell envelope or entirely secreted into the extracellular environment. The inner membrane (IM) contains three major transport systems for the translocation and insertion of signal sequence containing proteins: the Sec translocon, the YidC insertase, and the Tat system. The heterotrimeric SecYEG translocon forms a narrow channel in the membrane that serves a dual function; it allows the translocation of unfolded proteins across the pore and the integration of α-helical proteins into the IM. The YidC insertase is a multi-spanning membrane protein that cooperates with the SecYEG translocon during the integration of membrane proteins but also functions as an independent insertase. Depending upon the type of protein cargo that needs to be transported, the Signal Recognition Particle (SRP), the SRP receptor, SecA and chaperones are required to coordinate translation with transport and to target and energise the different transport systems. The Tat system consists of three membrane proteins (TatA, TatB and TatC) which in a still unknown manner accomplish the transmembrane passage of completely folded proteins and protein complexes.


*Keywords:* Sec-dependent pathway; Tat-dependent pathway; Inner membrane; Gram-negative bacteria; Protein translocation; Chaperone proteins

## 1. Introduction

One of the major challenges that prokaryotic and eukaryotic cells face is efficiently transporting proteins from their site of synthesis in the cytosol to their sites of function. As 20%–30% (Pugsley, 1993; Holland, 2010) of all proteins in bacterial cells are localised outside the cytosol, it is evident that protein transport is vital for the sustenance of cells. The inner membrane in Gram negative bacteria like *Escherichia coli* separates the cytosolic translation machinery from extra-cytosolic sections such as the periplasmic space or the outer membrane, forming a barrier against protein trafficking. To facilitate protein transport across this barrier, bacteria are equipped with membrane embedded protein transport systems that allow transport of proteins across the membrane into the periplasm or insertion of proteins into the membrane. There is a remarkable array of protein transport systems found in bacteria (Papanikou et al., 2007), but only three systems appear to be present in most bacterial species and are focused on in this review (Fig. 1):

a) The **Sec translocon** is the most characterised protein transport system and is thought to function as the major protein transport site in bacteria. It is present in all bacteria, archaea, and in the endoplasmic reticulum membrane of eukaryotic cells. It is also present in chloroplasts but absent in the mitochondrial membrane of most

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organisms, with the exception of the protist *Reclinomonas americana* and related protozoa (Tong et al., 2011). The Sec translocon has two functions; it transports secretory proteins across the inner membrane and inserts membrane proteins into the inner membrane. This dual role makes it functionally distinct from the YidC insertase, which has so far been shown to mainly aid the insertion of membrane proteins.

b) The **YidC insertase** is probably the simplest system for integrating membrane proteins into the cytoplasmic membrane (Dalbey et al., 2011). YidC is found in all bacterial species, many archaea and in bacteria-derived

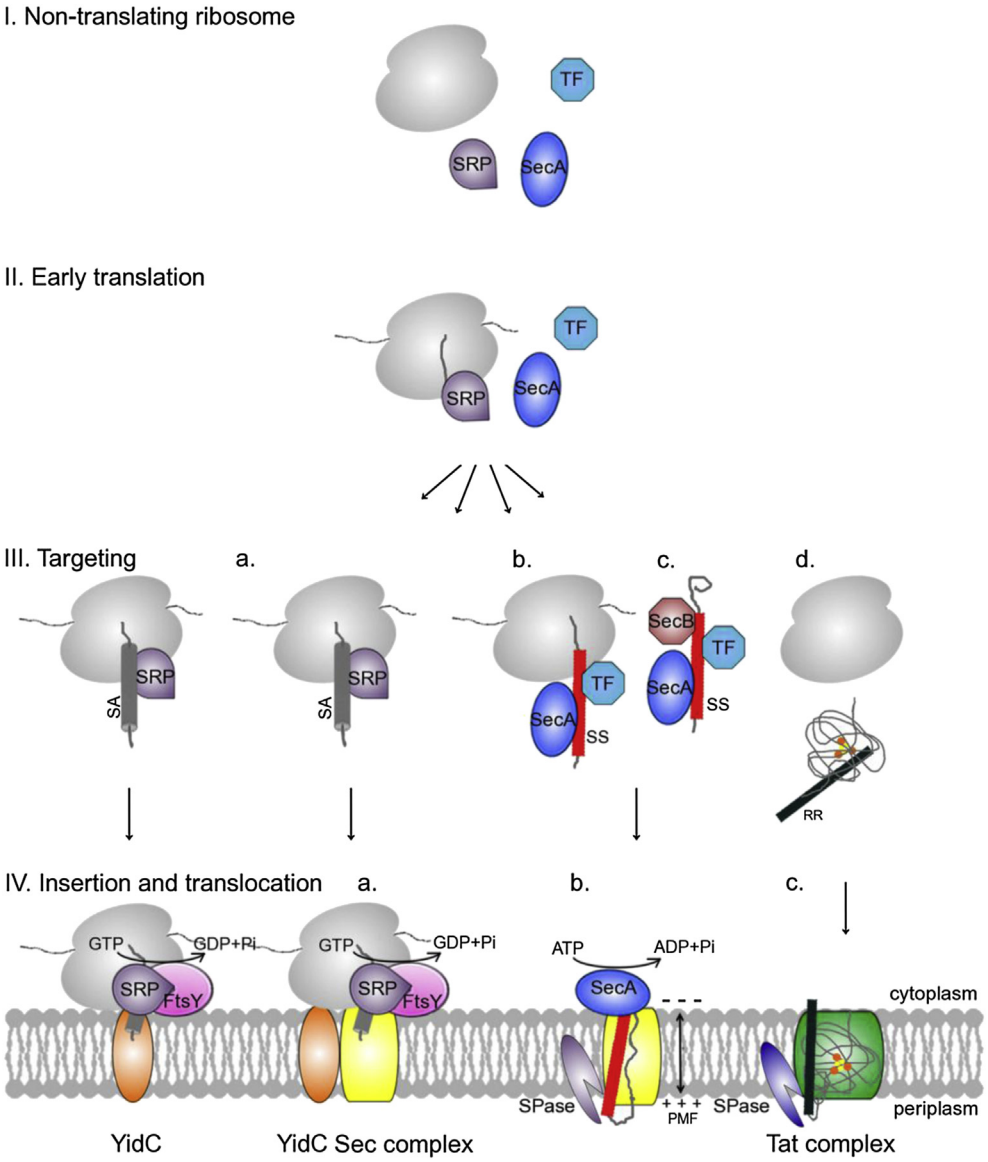


Fig. 1. Overview of the major protein transport pathways in Gram negative bacteria. I: Non-translating ribosomes have a basal affinity for the targeting factors SRP and SecA and for the chaperone Trigger Factor (TF). Whether all non-translating ribosomes have TF bound, as initially suggested (Deuerling et al., 1999) is questioned by recent data suggesting that TF binds preferentially to ribosome-associated nascent chains (RNCs) exposing at least 100 amino acids (Hoffmann et al., 2012). II: SRP has a high affinity for translating ribosomes. Although binding of SRP and TF to translating ribosomes appears to be non-exclusive, the coordination between SRP binding to RNCs and binding of other proteins like SecA or processing enzymes like peptide-deformylase (PDF) or methionine aminopeptidase (MAP) remains unclear. III: If a Signal Anchor (SA) sequence emerges from the ribosomal exit tunnel, SRP remains bound to the ribosome (3a) and targets the ribosome-nascent chain (RNC) complex to the membrane-anchored SRP receptor FtsY. If a signal sequence of a soluble protein (SS) is exposed in the growing nascent chain, SecA can replace SRP on the ribosome. Co-translational targeting starting with SecA binding to RNC (3b) is one of the two alternate targeting pathways, which have been suggested for secretory proteins. Another model (3c) favours post-translational targeting, where SecB holds the substrate in a translocation competent state with subsequent signal sequence recognition by SecA. The signal sequence of a protein transported via the Tat translocase contains a twin arginine motif (3d). The Tat complex exclusively transports folded substrates. However, signal recognition and targeting processes remain to be elucidated. IV: After targeting of an RNC by SRP, the RNC is transferred to the SecYEG translocon, YidC insertase, or to the complex of both. The SRP-FtsY complex is thought to disassemble upon GTP hydrolysis simultaneously with this event. Proteins with a SA sequence are laterally inserted to the lipid bilayer of the inner membrane (4a). Secretory proteins are translocated through the SecY pore with the aid of SecA, which acts as an ATP-powered motor (4b). Signal sequences of both Sec and Tat translocated proteins are removed in periplasm by inner membrane embedded signal peptidases (SPases).