CHAPTER 1

Protein Translocation Across the Endoplasmic Reticulum Membrane

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Abstract

Proteins to be secreted from eukaryotic cells are delivered to the extracellular space after trafficking through a secretory pathway composed of several complex intracellular compartments. Secretory proteins are first translocated from the cytosol into the endoplasmic reticulum (ER), after which they travel by vesicular trafficking via various intermediate destinations en route to the plasma membrane where they are released from the cell by exocytosis. By sharp contrast, secretion in prokaryotes involves the translocation of proteins directly across the plasma membrane. While these two systems are superficially dissimilar, they are evolutionarily and mechanistically related. This relationship between the prokaryotic and eukaryotic systems of secretion forms the backdrop for this chapter focused on protein translocation into the ER. In the first part of this chapter, the essential steps and core machinery of ER translocation are discussed relative to evolutionarily conserved principles of protein secretion. The last section then explores the concept of regulation, a poorly understood facet of translocation that is argued to be evolutionarily divergent, relatively specific to the ER, and likely to be most highly developed in metazoans.

Reductionistic View of ER Translocation

The eukaryotic secretory pathway is thought to have evolved by a series of steps that were initiated by specialization of the prokaryotic plasma membrane (Fig. 1). This specialized region of membrane was then expanded, internalized, and eventually subdivided into many compartments. Hence, the luminal space of compartments in the secretory pathway is topologically equivalent to the extracellular space, and the transport of proteins across the prokaryotic plasma membrane is directly analogous to transport into the ER. Both processes face the same basic challenges: (a) substrates to be transported need to be recognized, (b) selectively targeted to the site of transport, (c) vectorally translocated across the membrane, and (d) maintain a permeability barrier during these events. At the most fundamental level, these obstacles must have been solved in even the earliest life forms. This realization, together with the evolutionary relationship between the eukaryotic ER and bacterial plasma membrane, suggests a substantial conservation of the core principles of secretory protein translocation. Thus, assorted data using various model substrates from multiple systems (e.g., Bacteria, Archaea, yeast, and mammal)

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Figure 1. Evolution of the eukaryotic secretory pathway. Steps (1) through (4) depict successive stages in the generally accepted view of eukaryotic secretory pathway evolution from a prokaryotic ancestor. The cytoplasm is shown in gray, and translocons for protein secretion are depicted by cylinders with the direction of polypeptide transport indicated by an arrow. Note the relationship between secretion across the bacterial plasma membrane (in stage 1) and translocation into the ER (in stage 4). Diagram 4a shows a more detailed view of the mammalian secretory and endocytic pathways, with the primary pathways of protein traffic indicated by arrows. Essentially all of these pathways have been discovered to be regulated in a manner that allows some, but not other substrates to be trafficked in appropriate amounts to meet the changing demands of the cell. Notable examples include quality control at the ER, exit from the ER, sorting at the Golgi, regulated exocytosis, and endocytic sorting and degradation. By contrast, translocation into the ER (open arrow) is often regarded as a constitutive process where the presence of a signal sequence in a protein predetermines its entry into the ER.