

SIGNAL PEPTIDE HYPOTHESIS

Q.What do you mean by signal peptide hypothesis?

The signal hypothesis proposes that proteins destined for secretion, which involves the movement of the protein across a biological membrane, are originally manufactured with an initial sequence of amino acids that may or may not be present in the mature protein. Gunter Blobel and David Sabatini (1971) stated this hypothesis. **Blobel** and **Dobberstein** stated that the essential feature of the signal hypothesis is the occurrence of a unique sequence of codons, located immediately to the right of the initiation codon, which is present only in those mRNAs whose translation products are to be transferred across a membrane.

Q.Why ribosomes engaged in the synthesis of secreted proteins—attach to membranes, while ribosomes synthesizing cytosolic proteins do not?

- (a)mRNAs to be translated on membrane bound ribosomes contain a unique set of codons just 3' of the initiation site,
- (b)Translation of these codons yields a unique sequence at the amino terminus of the growing polypeptide chain (*the signal sequence*) and
- (c)The signal sequence triggers attachment of the ribosome to the membrane.

Q.Illustrate a model to explain the role of SRP on binding with signal sequence of a growing polypeptide and transportation of the synthesized polypeptide within ER lumen.

The signal sequences span about **20 amino acids**, including a stretch of **hydrophobic residues** usually located at the amino terminus of the polypeptide chain. As they emerge from the ribosome signal sequences are recognized and bound by a **signal recognition particle (SRP)** consisting of 6 polypeptide and a small Cytoplasmic RNA (srpRNA).

Figure1:A schematic model of the synthesis of a secretory protein (a lysosomal enzyme) on a membrane-bound ribosome of the RER.

STEP-1:As the signal sequence emerges from the ribosome, it binds to the SRP, which stops further translation until the SRP-ribosome nascent chain complex can make contact with the ER membrane.

STEP-2:The P-ribosome complex then collides with and binds to an SRP receptor, situated within ER membrane.

STEP-3:Attachment of this complex to the SRP receptor is followed by release of the SRP and the association of the ribosome with a translocon of the ER membrane. These latter events are accompanied by the reciprocal hydrolysis of GTP molecules bound to both the SRP and its receptor.

STEP-4:The signal peptide then binds to the interior of the **translocon**, displacing the plug from the channel and allowing the remainder of the polypeptide to translocate through the membrane cotranslationally

After the nascent peptide passes into the lumen of the ER, the signal peptide is cleaved by a membrane protein (the signal peptidase) and the protein undergoes folding with the aid of ER chaperones, such as BiP.

Q.What are the major kinds of proteins considered under signal peptide hypothesis?

The ER captures selected proteins from the cytosol as they are being synthesized. These proteins are :

Protein translocated	Features
Transmembrane proteins	Partly translocated across the ER membrane and are released into the ER lumen
Transmembrane proteins	Function in the ER but many are destined to reside in the plasma membrane or the membrane of another organelle.
Water soluble proteins	Destined either for secretion or for residence in the lumen of an organelle.

All of these proteins regardless of their subsequent fate, are directed to the ER membrane by an **ER signal sequence**, which initiates their translocation by a common mechanism.