Signal Hypothesis Encyclopedia Article

Signal Hypothesis

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Contents

Signal Hypothesis Encyclopedia Article.....1

Contents.....2

Signal Hypothesis.....3

Signal Hypothesis

The signal hypothesis was proposed to explain how proteins that were destined for export from **bacteria** or for targeting to certain regions within eucaryotic **microorganisms** (e.g., **yeast**) achieved their target. The hypothesis was proposed in the 1970s by Günter Blobel, who was then as now a molecular biologist at the Rockefeller University in New York. Blobel's work received the 1999 Nobel Prize in medicine or physiology.

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 present in the mature protein.

Work by Blobel and others over two decades established the validity of the proposal. The so-called signal sequence is now known to be only some 20 amino acids in length. The arrangement of amino acids in the signal sequence is not random. Rather, the beginning of the sequence, along with a few amino acid residues in the center of the sequence, is comprised of amino acids that are hydrophilic ("water-loving"). Sandwiched between these regions is a central portion that is made up of amino acids that are **hydrophobic** ("water-hating").

The hydrophilic beginning of the signal sequence, which emerges first as the protein is made, associates with the inner hydrophilic surface of the membrane. As the hydrophilic region of the protein merges, it burrows into the core of the membrane bilayer. The short hydrophilic stretch within the signal sequence anchors in the hydrophilic region on the opposite side of the membrane. Thus, the sequence provides an anchor for the continued extrusion of the emerging protein. In some proteins, the signal sequence can be enzymatically clipped off the remainder of the protein. Proteins of Gram-negative bacteria that are exported from the inside of the cell to the periplasmic space between the inner and outer membranes are examples of such processed proteins. Alternatively, the protein may remain anchored to the membrane via the embedded signal sequence.

The signal hypothesis has been demonstrated in plant cells, animal cells, single-celled **eukaryotes** (e.g., yeast), and in bacteria. The malfunction of the signal mechanism can be detrimental in all these systems. In contrast, the use of signal sequences has proven beneficial for the export of bio-engineered drugs from bacteria.