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Discovery of Intrinsic Signals in Proteins Governing Transport and Localization

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1999 Nobel Prize Medicine

Günter Blobel was awarded the Nobel Prize in Physiology or Medicine in 1999 for his discovery of intrinsic signals in proteins that govern their transport and localization in the cell.

The research conducted by Blobel was able to answer several questions that bothered scientists and molecular biologists during the 1970's. Blobel was particularly able to answer the question regarding the mechanisms behind the coordinated and properly directed flow of proteins within the different compartments of the cell and even the mechanisms by which proteins are transported out of the cell.

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Background On Cellular and Protein Function

Proteins are building blocks of life. Approximately 100,000 billion cells make up a human being. Each cell in a human body contains approximately one billion protein molecules. Each cell in our body also consists of functionally different parts. Cells have nucleus, endoplasmic reticulum, mitochondria, ribosomes and a lot more organelles which are lined by different membranes.

Each protein molecule must be able to learn how to navigate through the maze of organelles and membranes within a cell just to be able to perform its function. Prior to Blobel's discovery, we have little idea on how these billions and billions of protein molecules in our body are coordinated in such a way that they perform their specific functions properly.

Proteins are made up of 100 to 10,000 amino acids assemble into a chain that folds in itself to create a three dimensional distinct shape that is determined by the sequence of the amino acids. Proteins perform a variety of functions in the human body. It can be used as a building block or part of the different cellular membranes, it can be integrated into the myofibrils of our muscles and it can also act as an enzyme catalyzing the different reactions that are taking place within our body. An understanding of how these proteins are directed is vital to our wider understanding of life processes.

Günter Blobel

Günter Blobel was born on the 21st of May 1936 in Germany. He received his M.D. in 1960 from the University of Tübingen. He then earned his Ph.D. degree in Oncology from the University of Wisconsin when he worked with Van R. Potter in cancer research. He did his postdoctoral fellowship with Dr. Palade at the Rockefeller University. He rose from assistant professor to associate professor to professor in The Rockefeller University and in 1992; he was named John D. Rockefeller Jr. Professor. During his career, he earned numerous awards, some of which are US Steel Award in Molecular Biology, The Waterford Bio-Medical Science Award, The Warburg Medal of the German Biochemical Society and Albert Lasker Basic Medical Research Award.

Intrinsic Signals in Proteins

The research of Günter Blobel was focused on how a newly made protein, destined to be transported out of the cell, is targeted to an intracellular membrane system, the endoplasmic reticulum. His first working hypothesis was named "signal hypothesis" [1] wherein he postulated that proteins that are bound to exit the cell have intrinsic signals that direct their movements to and across membranes.

In the experiments that he conducted, he found that proteins that are destined to be exported out of the cell are synthesized by ribosomes that are attached to the endoplasmic reticulum. The information provided by the mRNA determines the composition of amino acids that will make up the protein. He also noted that a signal peptide is formed as a part of the protein that is being assembled. The signal peptide then binds to the signal-recognition particle or SRP. The SRP-ribosome complex then docks to the SRP-receptor and channel. The growing protein chain penetrates the channel and the SRP dissociates from the receptor. The completed polypeptide chain is released into the lumen of the endoplasmic reticulum and is subsequently delivered out of the cell.

In succeeding experiments, Blobel was also able to show that similar intrinsic signals in proteins are responsible for the transport of proteins to other intracellular organelles. He then concluded that each protein contains in its structure the information needed to direct its proper location in the cell. Furthermore, he postulated that specific amino acid sequences or topogenic signals determine the fate of the protein may it be bound for export out of the cell or become integrated into the membranes of the cell.

Clinical Correlation

Our knowledge about the intrinsic signals in proteins also known as topogenic signals has increased our understanding of several medically important mechanisms. It also helped us understand the basis of some human hereditary disease associated with errors in these signals and transport mechanisms. One example is the hereditary disease primary hyperoxaluria, which causes kidney stones at a very young age. Another disease is hypercholesterolemia which is a very high level of cholesterol in the blood. This disease was found to be due to deficient transport signals. Other hereditary diseases like cystic fibrosis are caused by the fact that proteins do not reach their proper destinations.

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Links

[1] <http://www.rockefeller.edu/research/faculty/abstract.php?id=225>