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Discovery of Reversible Protein Phosphorylation

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1992 Nobel Prize Medicine

Edmond H. Fischer and Edwin G. Krebs were awarded the Nobel Prize in Physiology or Medicine in 1992 for their seminal discovery of reversible protein phosphorylation and its importance as a biological regulatory mechanism.

Fisher and Krebs were able to show that reversible protein phosphorylation affects the structure, shape, function and activity of proteins that are responsible for the regulation of nearly all aspects of cellular life.

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Background

Proteins are one of the most important molecules in our body. Proteins are made of a chain of amino acids that have a distinct three-dimensional configuration. It is this unique three-dimensional configuration that dictates the molecular function of a protein.

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Background

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Each protein molecule within our bodies has a specific function. Proteins participate in metabolic processes, DNA replication, gene expression, and even in the cell cycle. Antibodies that are involved in defending our bodies from antigens are specialized proteins. The actin and myosin that are responsible for muscle contraction are also proteins. Enzymes that act as catalysts in our biochemical reactions are also made of proteins.

Some hormones like insulin, the hormone that regulates glucose metabolism, are also specialized proteins. There are also transport proteins like hemoglobin that carries oxygen through the blood. Another important process that dictates the function of proteins is phosphorylation. Phosphorylation refers to the addition of a phosphate to one of the amino acid side chains of a protein. Since it is the three-dimensional configuration of the protein that dictates its function, the addition of another phosphate molecule to the structure of the protein alters its function.

This means that if a protein undergoes phosphorylation, it undergoes a structural change via the addition of a phosphate which gives the phosphorylated protein another function.

The Winners

Edmond H. Fischer was born on the 6th of April 1920 in Shanghai, China. At an early age, he wanted to become a professional musician but his dreams changed during high school. He then studied in the University of Geneva and enjoyed chemistry and biology. He then worked on alpha-amylase for his Ph.D. in organic chemistry under Kurt H. Meyer. After his Ph.D. he went to University of Washington, Seattle due to an offer of Assistant Professorship in 1953. Six months after settling in University of Washington, he collaborated with Edwin Krebs on a research concerning glycogen phosphorylase.

Edwin Gerhard Krebs was born on the 6th of June 1918 in Lansing, Iowa. He attended Urbana High School and then enrolled at the University of Illinois at Urbana in 1936. During those years, his projected career path was towards organic chemistry or medicine.

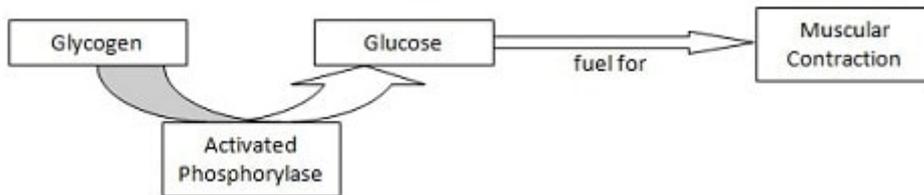
Krebs immediately chose medicine after receiving a scholarship to pursue medicine at Washington University School of Medicine in St. Louis. After earning his M.D. he studied biochemistry as a fellow to Carl and Gerty Cori who were working on rabbit muscle phosphorylase. In 1948, he accepted an offer to be an Assistant Professor of Biochemistry at the University of Washington, Seattle. Five years later, he collaborated with the new comer Edmond Fischer on their Nobel Prize winning research.

The Discovery

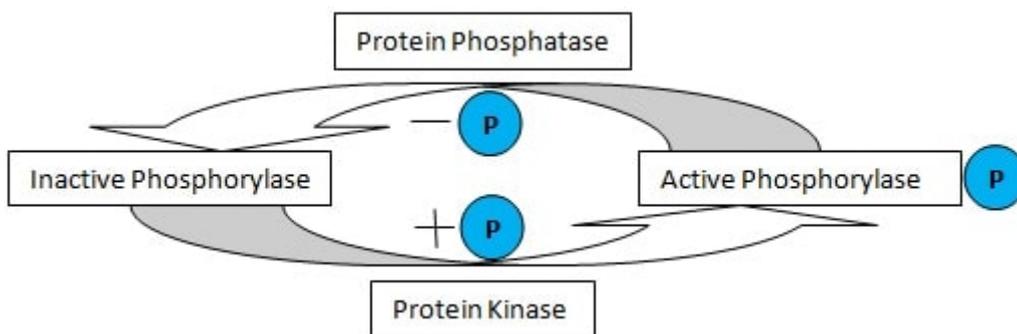
Together, Krebs and Fischer decided to see whether or not they could determine the mechanism by which 5'-AMP served as an activator of Phosphorylase B. They were not able

to solve that problem but in the course of trying, they encountered another astounding discovery. They discovered the molecular mechanism by which interconversion of the two forms of phosphorylase takes place which they called reversible protein phosphorylation.

Phosphorylase is the protein responsible for the breakdown of glycogen, our body's storage form of sugar and energy. If phosphorylases are activated, glycogen in our liver and muscles are broken down to glucose, the immediate energy supply of our muscles.



Fischer and Krebs found the mechanism by which phosphorylase is converted from an inactive form to an active form. They found that phosphorylase is activated by the addition of a phosphate group from an ATP which is an energy-rich compound, a form of phosphorylation. They also showed that this process is catalyzed by an enzyme called protein kinase. In addition, they also found the mechanism by which an active phosphorylase is converted to its inactive form. This process requires the elimination of the phosphate group and is catalyzed by the enzyme phosphatase, a complete reversal of phosphorylation. The discovery of these processes lead to the concept of reversible protein phosphorylation.



They also found that many of the proteins that are phosphorylated upon reception of a signal are protein kinases as well. This means that some proteins, after phosphorylation, acts as a protein kinase that will catalyze the phosphorylation of other proteins creating a phosphorylation cascade. They also noted that phosphorylation and reverse phosphorylation are regulated by a tightly guarded balance between phosphatases and kinases.

Importance of Reversible Protein Phosphorylation

The advantages of using reversible protein phosphorylation as a control mechanism in many cellular processes are:

- **Reversibility** – this means that the proteins and their functions can be regulated in both directions.
- **Amplification** – rapid and wide-spread protein action can be achieved via the phosphorylation cascade.
- **Conservation** – the reversibility of this process entails that the cell does not need to create new proteins or degrade existing proteins since their functions can be altered via

phosphorylation or dephosphorylation.

- **Regulation** - through the use of phosphorylation cycles and cascades, the cell is able to regulate a diverse set of processes, including cellular movement, reproduction and metabolism.

It is the simplicity, reversibility and flexibility of phosphorylation that explains why it has been adopted as the most general control mechanism of the cell.

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