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Role of G-Proteins in Signal Transduction

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1994 Nobel Prize Medicine

1994 was a revelation for both Alfred G. Gilman and Martin Rodbell for they were awarded the Nobel Prize in Medicine or Physiology for their discovery of the function and role of G-proteins in signal transduction. Their discovery explained how the information in the chemical signals is transduced by target cells upon the binding of the chemical signals to their respective receptors.

Gilman and Rodbell showed how a chemical signal that reaches the outside of the cell is interpreted and activates second messengers that can evoke changes in the inner machinery of the cell.

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Background

A single human organism is composed of billions and billions of cells. For the organism to survive, all the cells must be able to communicate effectively and act together as a single, unitary organism. Cells communicate with each other through chemical signals.

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In the 1950's and early 1960's, scientists already know that hormones, neurotransmitters and other forms of signaling molecules are released from cells. These signaling molecules are called first messengers. These first messengers then attach to their receptors in the target cell and the receptors will convert them to a signal that will act inside the cells. These signals are then called second messengers. They know that the conversion from first messengers to second messengers happen in the cell membrane but they didn't know any further.

Scientists were still unaware of the exact processes of signal transduction [1] happening after the binding of the first messengers to their respective receptors in the cell membrane.

The Winners

Alfred Goodman Gilman was born in 1941 in New Haven, Connecticut. His father, Alfred Gilman, is a musician and could play almost any kind of musical instrument. His mother was a pianist and gave regular piano lessons.

Despite this rich musical heritage, Alfred G. Gilman chose to become a chemist. This choice was triggered when his father turned to science and became a faculty of the Department of Pharmacology at Yale Medical School. His father authored a major book in pharmacology with his good friend Goodman which was published in 1941, the year Alfred Goodman Gilman was born. That may be the reason why he was named after the authors of the textbook, Goodman and Gilman. Gilman earned his B.S. in Biochemistry from Yale in 1962. He then enrolled in a combined MD/PhD program at Case Western Reserve University School of Medicine in Ohio where he studied under the mentorship of Theodore Rall. He then became a professor of pharmacology at the University of Virginia School of Medicine. He also became the chairman of the Department of Pharmacology at the University of Texas Southwestern Medical Center at Dallas.

Martin Rodbell was born on the 1st of December 1925 in Baltimore, Maryland. He finished his early schooling in Baltimore City College and enrolled in John Hopkins University majoring in Biology. He earned his B.S. in Biology in the year 1949. He then earned his Ph.D. in Biochemistry in the University of Washington in 1954. In the mid-sixties, he listened to a lecture given by Earl Sutherland on second-messengers and it caused him to do research on the cyclic AMP paradigm. In the late sixties and early seventies, he conducted his Nobel Prize winning research on the role of GTP and magnesium ions in hormone action.

The Discovery

Martin Rodbell was responsible for the entire conceptual framework of the receptor complex. He showed through a series of elegant experiments in the late 1960's and early 1970's that

signal transduction in the cell membrane of the target cell involves three important structures. He named the three structures as the receptor, the transducer and the amplifier.

The receptor is the structure responsible for the binding of the chemical signals to the cell membrane of the target cells. The receptor provides specificity to the receptor complex since chemical signals need corresponding receptors to ensure proper binding. The amplifier on the other hand is in the intracellular end of the cell membrane. It produces large amounts of second messengers like cyclic AMP or cAMP that activates different intracellular processes. Aside from these two structures, Rodbell was responsible for the introduction of the transducer structure.

The transducer is responsible for linking the receptor to the amplifier. Rodbell found that the transducer is driven by GTP or guanosine triphosphate, its source of energy.

Alfred G. Gilman, intrigued by the transducer concept of Rodbell, set out to determine the structure and composition of the transducer. He used mutated leukaemia cells in his experiments. He noticed that one mutated leukaemia cell with normal receptors and amplifier structures that generate cAMP as second messengers failed to respond to appropriate external stimuli. Because of this result, he hypothesized that the mutated leukaemia cells have dysfunctional transducer structure.

In 1980, Gilman was able to isolate and purify a protein that he thought was the transducer. He thought of this because when this normal protein was transferred to the cell membrane of the mutated leukaemia cells with dysfunctional transducers, the function of the receptor complex was restored. This protein was then named G-protein since it reacts with GTP at its driving force.

Structure, Function and Role of G-proteins in Signal Transduction

G-proteins are composed of three different proteins consisting of an alpha, beta and gamma subunits. The interaction between the receptor and the G-protein causes a transfer of a guanosine triphosphate or GTP for a guanosine diphosphate GDP on the alpha subunit. This means that when the receptor-G-protein complex is not activated, GDP is bound to the alpha subunit and during activation, GTP replaces the GDP. The GTP then activates the alpha subunit which causes the beta and gamma subunit complex to undergo a conformational change which allows them to separate from the alpha subunit. The beta-gamma subunit complex then interacts with another structure in the cell called adenylate cyclase. The interaction between the adenylate cyclase and the beta-gamma complex activates the adenylate cyclase to produce cyclic AMP or cAMP, the second messenger. The alpha subunit then hydrolyzes the GTP back to GDP which causes the beta-gamma complex to rebind with the alpha subunit. The G-protein is inactivated once again waiting for another wave of chemical signals.

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Links

[1] http://en.wikipedia.org/wiki/Signal_transduction