

Discoveries on the Key Regulators of the Cell Cycle

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2001 Nobel Prize Medicine

In 2001 Leland H. Hartwell, R. Timothy Hunt and Paul M. Nurse were awarded the Nobel Prize for Medicine or Physiology for their discoveries regarding the key regulators of cell cycle.

During that time, scientists and researchers all know that the cells in our bodies divide via cellular division but the mechanisms by which cellular division takes place was still unknown. They had no idea of specific proteins and signaling pathways responsible for the control and regulation of the cell cycle.



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Basics of the Cell Cycle

Scientists estimate that for every gram of tissue in our body, there are one billion cells in it. Can you imagine how many cells compose a single human adult?

All the cells in our body came from a single cell, the fertilized egg cell. During our physical growth, the single fertilized egg cell divides continuously until groups of cells finally make up a tissue, until groups of tissues finally make up an organ, and until a group of organs finally make up a living human. All these cannot be done if our cells are not capable of cellular division.

Cell cycle ^[1] or cell division cycle is the series of events that happens within the cell leading to its division. The cell cycle consists of several phases.

First is the G1 phase wherein the cell grows bigger until it finally reaches a critical size to enter the next phase, the S phase. During this phase, the genetic materials are duplicated and a copy of the chromosomes is formed. Next is the G2 phase wherein the cell checks if the duplication of the chromosomes is complete and there is further growth in the size of the cell. Next comes the M phase or mitosis phase wherein the cell divides to produce two identical daughter cells. Not all cells in the G1 phase automatically proceeds to the S phase, most of the cells exit the cell cycle and enters a resting phase or G0.

The Men Behind the Discovery

Leland Hartwell was born on the 30th of October 1939. During his childhood, he was an avid collector of bugs, butterflies, lizards, snakes and spiders. His major break was when he took the entrance exam on California Institute of Technology and he fell in love with the environment of real sciences. He graduated in 1961 and went to MIT for graduate school and he decided to work on gene regulation. He then became a professor in University of California and in the University of Washington.

Timothy Hunt was born on the 19th of February 1943 at Neston near Liverpool. He earned his B.A. in the University of Cambridge in 1964 and his Ph.D. also in the University of Cambridge.

Sir Paul Nurse was born on the 25 of January 1949. He earned his B.sc. in the University of Birmingham in 1970 and his Ph.D. in the University of East Anglia three years after. He became the Director-General of the Imperial Cancer Research Fund in London and became the head of the cell cycle laboratory.

The Seminal Discovery

Leland Hartwell was the pioneer of studying cell cycle using genetic methods. He made use of the yeast *Saccharomyces cerevisiae* as the subject of his experiments. In the year 1970, he tried to isolate individual gene that he thought were vital in the control of cell cycle.

Successfully, he was able to isolate cells wherein the cell cycle regulator genes were dysfunctional. By the use of this same method, he was able to isolate more than a hundred genes that were directly involved in the control of cell cycle. He called these genes CDC gene which stands for cell division cycle genes. Among the hundreds of CDC genes that he was able to isolate, he noted CDC28 gene for it was observed to control the first step of the cell cycle, progression from the G1 phase. For this function he named the gene, "start." He also introduced the concept of "checkpoints" wherein the cell cycle stops to check whether the DNA was perfectly duplicated.

The primary focus of the research of Sir Paul Nurse was to identify rate controlling steps in the cell cycle. He used a different type of yeast, *Schizosaccharomyces pombe*, as the subject of his experiments. In the 1970s, he discovered the CDC2 gene. With the help of his friend Pierre Thuriaux, they were able to prove that CDC2 gene was a rate limiting step controlling the onset of M phase.

On another study, he was trying to find a gene that also controls the transition from G1 to S phase similar to what Hartwell found. As a negative control for this experiment he used CDC2 mutants which he thought would block cell cycle progression from G2 to M phase. Surprisingly, his negative control always gave significant positive responses. He thought that his experiment was flawed and hypothesized that CDC2 was required twice in the cell cycle, first in the transition from G1 to S phase and from G2 to M phase. What he thought to be a faulty experiment turned out to be completely accurate.

Serendipitously, he found that CDC2 gene was also a rate limiting factor for the onset of S phase and M phase. In 1987, he also isolated the corresponding gene in humans which he called CDK1. This gene encodes for a protein that is a member of the cyclin dependent kinase CDK family.

In the early 1980s, Tim Hunt discovered the first cyclin molecule. He made use of another organism in his experiments, *Arbacia*, a sea urchin. In his experiments, he found strange bands with a basic behavior of strange disappearance which turned out to occur about 10 minutes before each cellular division. He called these bands cyclins because the levels of these proteins vary periodically during the cell cycle. Cyclins are proteins that are formed and then degraded during each cell cycle. This explains their varying levels.

The cyclins bind to the CDK molecules, thereby regulating the CDK activity and selecting the proteins to be phosphorylated. Cyclins have no catalytic activity and CDKs are inactive in the absence of its partner cyclin. When a CDK is activated by its partner cyclin, it activates or deactivates proteins that in turn control the entry of cells into the next phase of the cell cycle.

Clinical Implications

This discovery has great impact in cancer research. Chromosome alterations can be caused by faulty cell cycle control, defective S phase or uncontrolled cyclin-CDK activation. These chromosomal abnormalities are directly related to the development of cancer cells. Developments in the field of cancer diagnosis via this discovery include the fact that detecting increased levels of CDK-molecules and cyclins are sometimes found in human tumors like breast cancer and brain tumor. In the field of cancer therapy, inhibitors of CDK-molecules are now being tested for its effects in cancer treatment.

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