# Programmed Cell Death



### 2002 Nobel Prize Medicine

The Nobel Prize for Medicine or Physiology of 2002 was awarded to Sydney Brenner, H. Robert Horvitz and John E. Sulston for their discovery regarding gene regulation of organ development and programmed cell death or apoptosis.

Using the nematode Caenorhabditis elegans, the three scientists were able to identify genes that are responsible for regulation of organ development and apoptosis and they were also able to show that these genes are also present in more complex species like humans.



## Basics in Organ Development and Programmed Cell Death or Apoptosis

Everything starts with the union of the egg cell and the sperm cell to form an embryo. The fertilized egg will then undergo mitosis which will cause a rapid exponential increase in the number of cells in the developing embryo. Each cell will develop into a more specialized type of cell so that it can perform specific functions. An aggregation of cells performing similar functions is called a tissue. A group of tissues all directed to a common function is called an organ. Organ development is the process wherein individual cells develop into specific types of cells for them to be more equipped in performing the functions of their respective organs.

During the process of bodily growth, organ development and continuous cellular division which are all constructive processes, there is also a co-occurring destructive process called programmed cell death or apoptosis. Programmed cell death is a regulatory process to maintain the appropriate number and age of cells

present within a tissue. There must always be a balance between cellular division and cell death to ensure the viability of the species.

# The Researchers Who Contributed to the Discovery

Sydney Brenner was born on the 13th of January 1927 in Germiston, South Africa. He immediately became addicted with chemistry and collected test tubes and other glassware at home. He then decided to pursue medicine and took courses on Anatomy and Physiology. He became the director of Medical Research Council Laboratory of Molecular Biology in England.

H. Robert Horvitz was born on the 8th of May 1947. He finished his M.A. and Ph.D. in Biology at Harvard University. He then became a professor of Biology in MIT Cambridge and an Investigator in Howard Hughes Medical Institute, MIT. He also received numerous awards like Spencer Award in Neurobiology, U.S. Steel Foundation Award in Molecular Biology and Ciba-Drew Award for Biomedical Science.

John E Sulston was born on the 27th of March 1942. He is the son of an Anglican priest and a teacher of English. He got a scholarship to Merchant Taylors and immediately loved the sciences. He then studied at Cambridge with another scholarship. In 1963, he finished his B.A. at the University of Cambridge. Three years after, he finished his Ph.D. in the same university.

# Contributions to the Discovery

## Sydney Brenner and C. Elegans

Sydney Brenner was the pioneer of the entire series of researches. He was the one who established Caenorhabditis elegans [1] as the ideal and most suited organism for their experimental trials. He thought that if he wanted to observe organ development and cell death, he cannot use unicellular models like yeast and bacteria since it is very difficult to study organ development and the interplay between different cells in such organisms. Furthermore, he noted that using mammals in his study will also be difficult since the organism is too complex and there is enormous number of cells that must be studied. He wanted to limit his study to a manageable organism and he chose to use the nematode C. Elegans since it is not too complex or too simple.

The worm is approximately 1mm long, has a short generation time and is transparent allowing direct viewing of cell division under the microscope. In his studies in the early 1970s, he was able to show that specific gene mutations can be induced in the genome of the worm by using the chemical EMS or ethyl methane sulphonate. By the use of this method, he was able to induce specific gene mutations that caused direct effects on organ development.

## John Sulston and C. Elegans Cell Lineage

A few years after the study of Brenner on C. elegans, John Sulston developed techniques to view the process of cellular division from the fertilized egg of C. elegans to the 959-cell adult worm. He specifically targeted the development of the nervous system of the worm. He was able to conclude that the cell lineage is invariant. This means that all the worms he observed underwent exactly the same process of cell division and differentiation. He also noted that during the process of cellular differentiation, there is a co-occurring cellular death that is tightly regulated by the organism. Furthermore, he was able to distinctly identify steps in cellular death and a gene that participates in programmed cell death [2], nuc-1 gene. His succeeding studies showed that the nuc-1 gene was responsible for the degradation of the genetic materials in the dead cell.

### Robert Horvitz and a Genetic Program Controlling Death

Robert Horvitz followed up on the discoveries of Brenner and Sulston. He wanted to know if there is an internal genetic program in every cell that controls programmed cell death or apoptosis. In his investigations on C. elegans, he found that ced-4 and ced-3 genes participate in the execution of cellular death. These are the two death genes that he was searching for. He also found that every cell needs a functional ced-3 and ced-4 to undergo programmed cell death. Moreover, he also showed that ced-9 gene acts as an inhibitor to the two death genes. One of his most stellar contributions was proving that there exists a ced-3 like gene in the genome of humans. This entails that the death genes he found in the genome of C. elegans can possible have counterparts in our own genome.

## Clinical Applications

One of the most obvious applications of this discovery is the control of cancer development. Numerous researches are being conducted to discover ways to control the activities of these genes. If we can develop a technology that can stimulate death gene activity in cancer cells, this may provide us a way to cure cancer. If we can also learn how to stimulate ced-9 gene activity, we can address neurodegenerative problems that are characterized by massive cellular death.

These technologies or drugs can lead to the survival of cells that are normally destined to die. Lastly, these discoveries proved to be very important in the field of medical research especially in the pathogenesis of many diseases.

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**Links**
[1] http://sandwalk.blogspot.com/2008/09/nobel-laureates-sydney-brenner-robert
[2] http://en.wikipedia.org/wiki/Programmed_cell_death