Discovery Of Split Genes

1993 Nobel Prize Medicine

Similar to the context of most Nobel Prize winning researches, the discovery of Richard J. Roberts and Phillip A. Sharp regarding split genes contradicted the widely accepted scientific norm of the 1970's.

Rob were able to provide evidences that genes in higher organisms do not present as single, continuous strand in the DNA but rather, the genes present as several, well-separated segments. For this discovery, Roberts and Sharp were awarded the Nobel Prize in Medicine or Physiology in 1993. Their discovery led to a deeper understanding in the field of molecular biology and triggered researches concerning the development of different diseases.

Background

DNA is the hereditary material in humans and almost all living organisms. It is composed of four bases adenine, guanine, cytosine and thymine. The order of these bases determines the information that the DNA contains. A gene is a stretch of DNA that contains detailed instructions on how to build proteins. This instruction is first copied from the DNA to messenger RNA or mRNA.
The information in the mRNA is then decoded in the ribosome wherein amino acids are assembled to form proteins. Decoding of the mRNA entails that the individual bases in the mRNA were read three at a time, each triplet of bases corresponding for a single amino acid. The gene coding for a specific protein is surrounded by sequences of DNA that tells an enzyme called RNA polymerase where to begin transcribing the RNA and where to stop. The signal that tells where to start making RNA is called the promoter.

In the 1970's, molecular biologists believed that genes present in a single, continuous strand in the DNA. This was challenged by the discoveries of Roberts and Sharp which showed that genes present in a separated manner.

The Winners

Richard J. Roberts was born on the 6th of September 1943 in Derby, England. As a child, he initially wanted to become a detective but this immediately changed when he received a chemistry set as a present and knew he wanted to become a chemist. He then enrolled at Sheffield University due to their excellent chemistry department and graduated in 1965.

Fresh from college and just two years post-doctoral work at Harvard, Roberts was invited by Jim Watson to join him at Cold Spring Harbor Laboratory, where they worked together for more than two decades. Earlier in 1972, Roberts attended a seminar at Harvard Medical School given by Dan Nathans where he learned that an enzyme could cleave DNA into specific pieces. By the use of this enzyme, he began to map the DNA that lead to his Nobel Prize winning discovery.

Philip A. Sharp was born on the 6th of June 1944 in Falmouth, Kentucky. His early education was in McKinneysburg Elementary, Butler Elementary and High School and Pendleton County High School. He then enrolled at Union College and majored in chemistry and mathematics and decided that he wanted to continue learning about science, particularly chemistry.

Sharp was offered a fellowship and soon began graduate studies under Victor Bloomfield in physical chemistry. He completed his Ph.D. in chemistry at the University of Illinois in 1969. He then worked at the California Institute of Technology until 1971. After Caltech, he studied gene expression in human cells at the Cold Spring Harbor Laboratory under the mentorship of Jim Watson.

The Discovery

Roberts and Sharp wanted to know if the promoter sequence, the sequence of DNA that tells where to start making the RNA, of higher organisms is similar to the promoter sequence in bacteria which was relatively well-known during that time. They used an upper respiratory virus that grows in human cells called Adenovirus-2.

Roberts and Sharp began to develop methods whereby they could map the exact start of the mRNA sequences made from Ad-2 mRNA. They thought that if they could work out the sequence of the mRNA right to its very start, then they would merely need to locate the corresponding DNA sequence, identify the DNA sequence that preceded it and they have the promoter. To accomplish this, they developed a technique that allowed them to catch short
sequences from the very start of the Ad-2 mRNAs.

Considering that there are many different mRNAs that Ad-2 creates, they were expecting to find 15-20 different promoter sequences which code for the different mRNAs. They were surprised when they found that there is only one sequence for all the mRNAs and that the main parts of the mRNA were encoded a long way apart from its very start.

By using electron microscopy, they were able to show that the genes in Ad-2 were indeed split into pieces. They found that a single mRNA molecule corresponded to no less than four well-separated regions in the DNA molecule. For these discoveries, they concluded that genes present in multiple, well-separated strands in the DNA molecule, split genes have been discovered.

**Clinical Correlations**

To give you a better picture of what Roberts and Sharp discovered, consider the figures shown below. The shaded area corresponds to the genes and the white area corresponds to unrelated DNA strands. In the bacteria, the gene presents as a single, continuous strand in the DNA molecule. However, in the Adenovirus-2 and in higher organisms including man, they found that the gene presents in a fragmented manner. A gene thus consists of several fragments called exons (shaded areas) separated by intervening DNA called introns (white areas).

The consequence of split gene discovery is that the first RNA product produced by the gene which still contains both exons and introns, needs to be edited such that the introns are eliminated from the mRNA and the exons are coupled together to form a shorter mRNA.

Split gene discovery also helped us understand how several diseases arise. An example of which is a form of anemia called thalassemia. This disease is due to inherited defects in the genetic material. These genetic defects cause errors in the editing process of the mRNA causing a formation of an abnormal messenger RNA.

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