

Nobel Prize in Medicines 1978



Werner Arber



Daniel Nathans



Hamilton O. Smith

The Nobel Prize in Physiology or Medicine 1978 was awarded jointly to Werner Arber, Daniel Nathans and Hamilton O. Smith "for the discovery of restriction enzymes and their application to problems of molecular genetics"

Restriction enzymes provide the "chemical knives" to cut genes (= DNA) into defined fragments. These may then be used (1) to determine the order of genes on chromosomes, (2) to analyse the chemical structure of genes and of regions of DNA which regulate the function of genes, and (3) to create new combinations of genes. These techniques open up new avenues to study the organisation and expression of genes of higher animals and to solve basic problems in developmental biology. In medicine, increased knowledge in this area should help in the prevention and treatment of malformations, hereditary diseases and cancer.

Arber discovered restriction enzymes. He postulated that these enzymes bind to DNA at specific sites containing recurring structural elements made up of specific basepair sequences.

Smith verified Arber's hypothesis with a purified bacterial restriction enzyme and showed that this enzyme cuts DNA in the middle of a specific symmetrical sequence. Other restriction enzymes have similar properties, but different enzymes recognize different sequences.

Nathans pioneered the application of restriction enzymes to genetics. He demonstrated their use for the construction of genetic maps and developed and applied new methodology involving restriction enzymes to solve various problems in genetics.

This year's Nobel Prize in medicine or physiology is awarded for discoveries with far reaching consequences for genetics. The task of genetics is to describe and explain how genes are organized and expressed in cells and in living organisms. The discovery of restriction enzymes provided new tools for the detailed chemical analysis of the mechanism of gene action. Even though these enzymes have been available only during a few years their application to genetics has already led to new and far reaching results, in particular concerning the organisation and expression of genes (= DNA) of higher animals. All work in this area carried out by many research groups all over the world, is based on the discoveries made by the three laureates.

Restriction enzymes are used as tools to dissect DNA into smaller defined fragments. These can be used to determine the order of genes on chromosomes, to analyse the chemical structure of genes and to recombine genes by chemical means. Most important restriction enzymes are used to analyse the function of regions of DNA which regulate gene expression. This opens up new areas of research to study the connection between heredity and function. We can now begin to answer questions of central biological importance in developmental biology: how do genes direct the evolution of a single fertilized egg to a complete individual with many different organs? What determines that the cells within one organ normally retain their specialized functions? Different diseases are expressions of disturbances in normal functions and increased knowledge in molecular genetics should aid in preventing and treating malformations, hereditary diseases and cancer.

Werner Arber started this field of research in Geneva during the 1960's. He discovered restriction enzymes. Arber was studying an earlier known phenomenon, "host controlled restriction of bacteriophages", and found that this process involved changes in the DNA of the virus. The process apparently served to form a barrier against foreign genetic material. Arber showed that the phenomenon could be divided into two components: restriction and modification. Restriction involved a breakdown of DNA, modification was a change (= methylation) of DNA which prevented restriction. Arber postulated that both processes are catalyzed by specific restriction and modification enzymes. He proposed that DNA molecules contain specific sites with the capacity to bind both types of enzymes. These sites are created by recurring structural elements formed from specific basepair sequences. The enzymes act at these sites either by cleaving the molecule (= restriction) or by methylating it (= modification).

Hamilton Smith verified Arber's hypothesis. He is a biochemist and worked independently of Arber in Baltimore. In 1970 he published two classical papers which described the discovery of a restriction enzyme from the bacterium *Haemophilus influenzae* and characterized in detail the mechanism of its action. Other scientists before Smith had unsuccessfully tried similar experiments. The restriction enzyme from *Haemophilus influenzae* degrades foreign DNA to large fragments, about 1000 basepairs in size, but does not touch the DNA of the host bacterium. Most important, Smith showed that all fragments at their beginning and end had the same three basepairs showing that the enzyme had cleaved DNA wherever a specific sequence of 6 basepairs was present. This sequence was internally symmetric and was cleaved in the middle. Many other restriction enzymes have by now been characterized by others using the methodology worked out by Smith. More than 100 such enzymes are known and in most cases the same pattern is observed: a restriction enzyme recognizes certain symmetrical basepair sequences and cleaves DNA wherever these sequences occur. Different enzymes recognize different sequences and by now a battery of enzymes is available which can be used to cleave DNA at different sites in order to produce a multitude of defined fragments.

Dan Nathans pioneered the application of restriction enzymes to problems of genetics. He works in Baltimore at the same university as Smith. All his contributions in this area of research were made during the 1970's. Nathans uses in his experiments the small DNA from a simian virus, called SV40, but his results are of general significance. In his first communication from 1971 he showed that the restriction enzyme discovered by Smith cleaves SV40 DNA into 11 well defined fragments. In this communication Nathans also discussed other possible applications of restriction enzymes in genetics and in a brilliant way predicted much of the later development. Nathan's publication from 1971 no doubt served as a major source of inspiration for scientists who subsequently started to use restriction enzymes. Two years later he described the cleavage patterns of SV40 DNA obtained with two additional restriction enzymes. He could then piece together the fragments obtained from the three cleavages and construct the complete genetic map of SV40 DNA, the first obtained by a chemical method. The general approach designed by Nathans for SV40 was later used by other scientists for mapping increasingly complex DNA structures. The map of SV40 DNA was further refined by other scientists. Today we know the complete nucleotide sequence of the molecule and thus can write the complete chemical formula for all the genes of an animal virus. Nathans himself continuously contributed new ideas and developed new methods for the application of restriction enzymes to genetic problems and has continuously been a main source of inspiration in this field of research.

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