"Life Science" field

Achievement : Discovery of histone modifications as fundamental regulators of gene expression

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Summary

A human body consists of approximately 60 trillion cells, and most of them have the same genetic information in DNA (deoxyribonucleic acid). How can cells with the same DNA develop into many different types of cells to make up the different organs in the body with different forms and functions, such as skin, liver and cranial nerves? A biochemist from the U.S., Dr. David Allis, tackled this question and discovered from his research in the 1990s that enzymes that chemically modify histones, proteins found in chromosomes, play a vital role in the regulation of gene activity. His findings have greatly contributed to the understanding of the generation mechanism in which an organism grows from a fertilized egg, as well as to the development of drugs to treat cancer related to abnormalities in histone modifications.

How do various organs result from cells with the same genetic information?

DNA, which is found within the cell nucleus of living organisms, is called "the blueprint of life." Ever since the double helical structure of DNA was discovered by James Watson and Francis Crick in 1953, scientists have been endeavoring to explain how life phenomena are brought about by means of the information written in the DNA. In the 1990s, the Human Genome Project commenced with the goal of decoding the entire base sequence (genome) of the human DNA and was completed in 2003, 50 years after the discovery by Watson and Crick.

Is it possible to understand all about life phenomena if the base sequence of DNA is defined? Unfortunately, the answer is "no." While the Human Genome Project was in progress, it was becoming clear that, in addition to the genetic information of the DNA, there exists a mechanism in which a part of the genetic information is selectively expressed at each cell level and that this system is extremely vital in life phenomena.

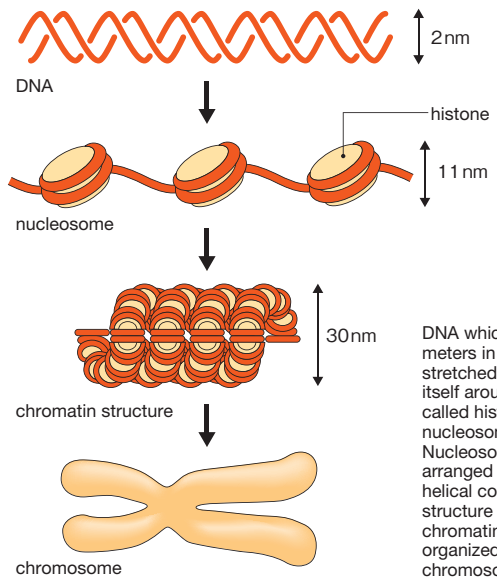
For example, in the human body, there are approximately 300 types of cells, and with the exception of a small fraction, most have the same DNA. Despite having the same DNA, they develop into different types of cells with different forms and functions, such as skin cells and hepatic cells. The characteristics of these cells carry on even after cell division.

The academic field which studies chromosomes controlling mechanisms without changes in DNA sequences is called epigenetics. Epigenetics has several research themes, such as a phenomenon known as "DNA methylation." Dr. David Allis was the first to clarify in 1996 that a chemical modification known as acetylation occurs on histones, proteins which constitute the chromosomes in eukaryotes (organisms having a nucleus within the cell), and that such modifications are relevant to the controlling of gene expression. His discovery has made a significant contribution to the development of the emerging science of epigenetics.

Fascinated by Real Lab's appeal, taking on the challenge of the mechanism of the genetic expression control

Dr. Allis was born in Cincinnati, a major city in southwestern Ohio, the United States, in 1951. After graduating from high school, he entered the University of Cincinnati. He majored in biology in preparation for medical school. However, his advisor suggested that he experience basic research (Dr. Allis refers to this as the Real Lab), which is another forefront indispensable to the development of medicine. He ended up becoming engrossed with this basic research, in particular embryology, and acquired a doctorate degree in biology at the postgraduate school of the University of Indiana in 1978.

Figure 1 : DNA folding structure



DNA which extends to 2 meters in length when stretched out, wraps itself around proteins called histones to form a nucleosome. Nucleosomes are further arranged in a stacked helical complex to form a structure called chromatin, which is organized to form a chromosome.

He then moved on to the University of Rochester and made the University of Virginia Health System his research base. There, he conducted research on the functions of chromosomes using various organisms such as drosophila, but eventually focused his research subject on a unicellular organism called tetrahymena. The cell nucleus of tetrahymena is divided into a micronucleus and a macronucleus. The micronucleus is not active normally, but carries on through cell division similar to a reproductive cell of a higher organism, and cell activity is carried on based on the DNA of the macronucleus.

In the 1990s, Dr. Allis chose histones, proteins that constitute the chromosomes of tetrahymena, as the essential study theme of his research group. What, then, is a histone? The DNA in our cells becomes approximately two meters in length when stretched out. Histones organize "long strands" of DNA into a cell nucleus just 10 micrometers in diameter in a compact and orderly fashion. DNA coils itself around granular histones approximately two times to form a nucleosome. Nucleosomes are further arranged in a stacked helical complex to form a structure called chromatin, which is organized to form a chromosome (Figure 1).

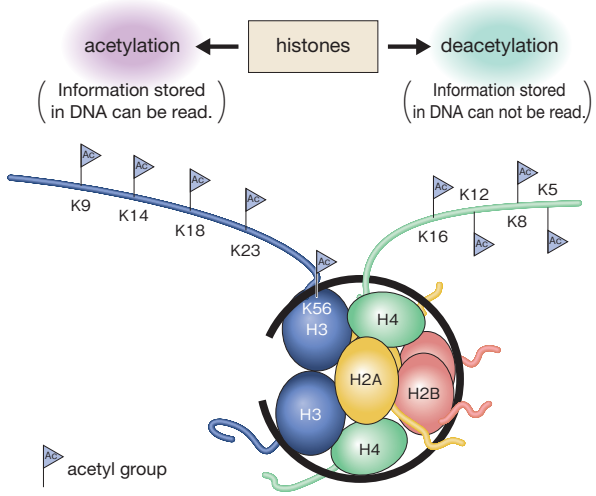
What the researchers particularly paid attention about histones was that the region within the DNA which is not used in cell activity is bound strongly to histones. Conversely, when the base sequence information is being used, the DNA distances itself from histones, in a loosely unbound state. What substance regulates the bond between the DNA and histones? Dr. Allis' research team continued to undertake the challenge of clarifying the difference between chemical modifications in the macronucleus and the suspended action in the micronucleus when tetrahymena is active.

There proved to be stiff competition developing among research groups worldwide. Finally, in 1996, it was clarified that with histones in the region where genetic information could be read, histone acetyltransferase which binds itself to the acetyl group is active. In addition, through the balance between the histone acetyltransferase and the histone deacetylase, genetic expression is regulated, thus proving for the first time that changes in the chromatin structure through histone modifications are actually regulating gene activity.

Study of histone modifications contributes to the development of next-generation medicine

The discovery by Dr. Allis' research group served as a catalyst for the rapid development of studies related to chromosome functions.

Figure 2 : Histone tails and acetylation



Histones form a structure known as a histone octamer in which eight small proteins are bound together. Several proteins have a tail, and when an acetyl group is attached to the tail, DNA binding to histones is regulated.

It also clarified that not only the acetyl group but several other substances such as the methyl group also attach themselves to histones (chemical modification). When probing into the histone structure, there are eight small ball-like proteins connected together in a form called a histone octamer, with some proteins having a "tail" extension. A "histone code hypothesis," in which it is thought that multiple chemical modification patterns connected to the tail function as a "code," controlling the gene expression, has been proposed, and studies thereof are ongoing (Figure 2).

Dr. Allis' research is also contributing to the progress of medicine. For example, it has come to light that not only gene abnormalities but also abnormalities in epigenetics such as histone modifications contribute to the occurrence of cancer. There has been one report after another of histone acetylation decrease in certain types of cancer, and molecular-target drug named HDI (histone deacetylase inhibitor) which repairs the balance between histone acetylase and histone deacetylase has been proposed. With "Vorinostat," the first HID for cutaneous T-cell lymphoma approved in the U.S. in 2006, studies of several new drug candidates are underway.

In addition, histone modifications play a major role in governing the occurrence of organisms, contributing to the progress of regenerative medicine using iPS cells. The research into histone chemical modifications pioneered by Dr. Allis, will continue to be a vital field in the future development of life science.