"Bioscience and Medical Science" field

Achievement: Discovery of interleukin-6 and its application in treating diseases

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Summary

Our bodies detect external invasions of bacteria and viruses and eliminate them. This mechanism is called "immunity." Immunity is a complex system consisting of various cells such as lymphocytes (T-cells, B-cells) and macrophage, but the substance which plays an important role in transmitting information between cells is called interleukin. Dr. Tadamitsu Kishimoto and Dr. Toshio Hirano have purified interleukin 6 (IL-6), which plays a vital part in the production of antibodies, and also succeeded in gene cloning in 1986. In addition, the two doctors have identified a wide range of functions of IL-6 and their research results have contributed to the progress of bioscience and the development of therapeutic drugs for inflammatory diseases.

In quest of a substance which transmits immune cell commands

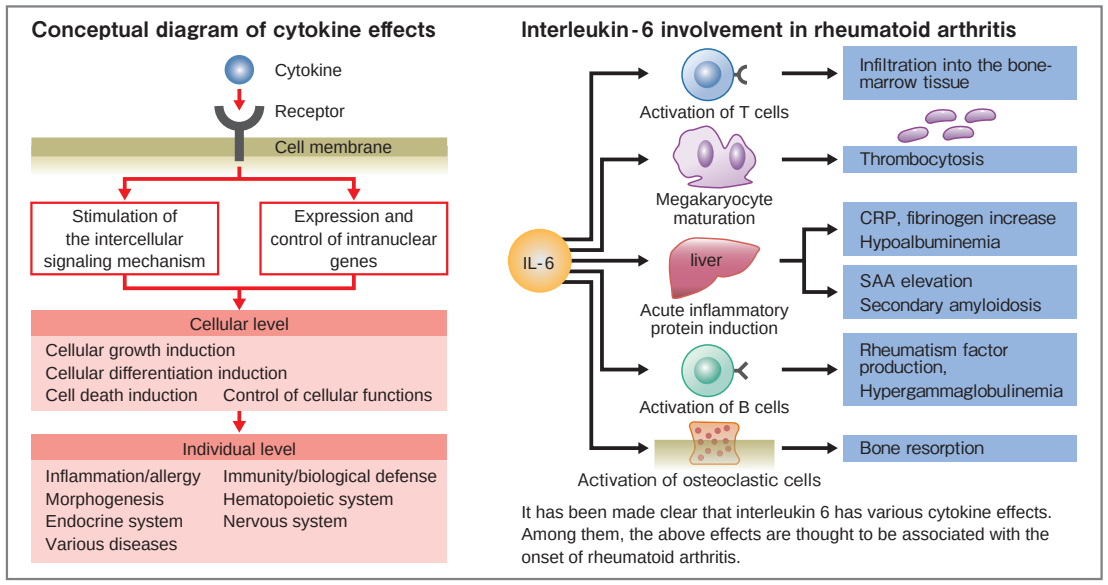
The knowledge that the human body has an immune system which, once exposed, builds in us resistance to a certain illness, has been long-established. Modern medicine started off with researchers confronted with the challenge of revealing what the immune system is. At the end of the 19th Century, Shibasaburo Kitazato and German physician Behring conducted research on the serum therapy of tetanus and diphtheria and discovered that a substance which attacks the pathogen is formed within the body once we are exposed to such infectious diseases. Thus, the concept of the immune system where the antibodies recognize and eliminate antigens was established. Around the same period, Russian microbiologist Mechnikov claimed that leukocytes within the blood attack pathogens such as bacteria in a mechanism called "phagocytosis," thus establishing the foundations of immunology.

Coming into the 20th Century, the characteristics of antibodies as substances were clarified and in a wider sense, the immune system came to be identified as a complex system made up of a wide variety of cells including companions of leukocytes such as lymphocytes, macrophage and dendritic cells. It was not until the late 1960's that the research regarding the essence of the immune system proceeded rapidly. It was then discovered that there were two types of lymphocytes, namely T-cells and B-cells, and that it was by mutual transmission of information between these two cell types that enabled the various antibodies to be produced efficiently. By defining the signaling mechanism, knowledge about the complex immune system can be acquired. The protein used to transmit information among the cells is called cytokine, and among these, interleukin is the substance most closely connected to the immune system. It was the study of interleukin which researchers around the world were competing to undertake.

It was immunology, a field in which cutthroat competition was already underway, that Dr. Kishimoto who graduated from Osaka University, Graduate School of Medicine, in 1969, decided to aim for. The catalyst for his decision was in his 5th year of medical school when he heard the lecture by the late Yuichi Yamamura, a pioneer in immunological research in Japan. He was intrigued by the discourse about autoimmune disorders where the immune system, which should protect our bodies from pathogens, revolts and attacks our bodies.

Dr. Kishimoto studied for 4 years from 1970 at the Johns Hopkins University in Baltimore, U.S., under Professor Kimishige Ishizaka (the 2000 Japan Prize Laureate), who discovered immunoglobulin E. After returning to Japan, he became an assistant at Osaka University, Faculty of Medicine, and in 1975, he was able to do research for 3 months under Robert Good, the Director of Laboratory at the Memorial Sloan-Kettering Cancer Center, who was closely following Dr. Kishimoto's research. During that short period, he discovered a new interleukin candidate substance which generates from T-cells and creates antibodies within B-cells. The research results thereof were posted and published in a British science magazine "Nature."

Figure Functions of lymphocyte-produced interleukin-6



It has been made clear that interleukin 6 has various cytokine effects. Among them, the above effects are thought to be associated with the onset of rheumatoid arthritis.

Success in gene cloning after much hardship

All seemed smooth sailing, but it was only the beginning of research for Kishimoto. The characteristic of cytokine is that one type has many combined functions, and there are many companions with overlapping functions. Even if the biological activities of the discovered substance were studied, it would be difficult to prove whether it was really a new substance. The academic society only acknowledged a new substance if the gene which creates a substance is extracted singularly (cloning).

What provided a boost to Dr. Kishimoto who was in search of the gene of the discovered substance, was the establishment of the Institute for Molecular and Cellular Biology at Osaka University in 1982, which became the center of bioscience. In the following year, Dr. Kishimoto, who became a professor at the above institute, welcomed Dr. Hirano as his research partner. Dr. Hirano graduated the Faculty of Medicine at Osaka University and went on to study immunology at the National Institute of Health (NIH) at Baltimore, U.S., so they had been acquaintances from their days in the U.S. Moreover, Dr. Hirano, after returning to Japan, had been continuing his research at Habikino Hospital and the School of Medicine at Kumamoto University, and had independently discovered interleukin and was working on the cloning.

Both doctors adopted the leading-edge genetic engineering techniques and continued in their gene hunt. They were unable to obtain the desired results, and continued in their low-profile experiments for days and then for years, often struggling with frustration. However, in May, 1986, they finally succeeded in capturing a particular gene. In 1988, at the international conference, the name interleukin 6 (IL-6) which meant that this was the 6th interleukin that the two professors cloned, was given.

Application of research results to the therapeutic drug for rheumatoid arthritis

After the success of gene cloning, by means of the genetic modification technique, a highly pure IL-6 was obtained, and progress was also seen in the clarification of its mechanism. The research group with both doctors as core members also identified the structure of the IL-6 receptor. In addition, they explained the intracelluar signals which transmit IL-6 information to the cell nucleus. By publishing various articles about the IL-6 mechanisms one after another, they became the world's leading researchers in this field.

What proved fortunate for both doctors was that as the research progressed, it became evident that IL-6 not only enhances antibody production, but also has a wide variety of functions. For example, it has a mechanism for stimulating the production of protein within the liver (CRP) when an acute inflammation occurs in the body. It also has a mechanism for increasing platelets within the blood components which coagulate blood in the event of an injury. There is also a mechanism for thickening heart muscles. The more research is done, the more functions are discovered, thus contributing to the progress of medicine.

Particularly noteworthy was the discovery that IL-6 is involved in the onset of rheumatoid arthritis, which is representative of autoimmune disorders. The two doctors had already noted from an early stage of their research that IL-6 is deeply involved in the inflammatory reactions within the body, but it was newly discovered that a large quantity of IL-6 exists in the joint fluid of rheumatoid arthritis patients. From this discovery, an important result was obtained about its pathogenic mechanism.

Both doctors are currently involving themselves diligently in research activities. Dr. Kishimoto, based on basic research, has jointly developed, with a pharmaceutical company, an antibody drug Tocilizumab which inhibits IL-6 action. After being approved in Japan in 2008, the drug has become approved in 70 countries worldwide including Europe and U.S. Dr. Hirano defined the mechanism of the onset of autoimmune diseases in addition to discovering that IL-6 plays a vital role in the initial stage of the emergence of fish. Research originating from the discovery of IL-6 has broadened its horizons from leading-edge medicine to bioscience.