"Medical Science and Medicinal Science" field

Achievement : Discovery of B and T lymphocyte lineages and its impact on understanding disease pathology and therapeutic development

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Summary

Dr. Max D. Cooper and Dr. Jacques Miller discovered the "B and T lymphocytes", the two primary cell lineages involved in adaptive immunity that are responsible for protecting our bodies from intrusion by foreign substances. The B lymphocytes are responsible for the production of antibodies that attack foreign substances such as invading pathogens. T lymphocytes, on the other hand, are responsible for attacking virus-infected cells and cancer cells, and assisting B lymphocytes in the production of antibodies. Using mice, Dr. Miller discovered that T lymphocytes are produced by the thymus, which was considered a vestigial organ at the time. Dr. Cooper, on the other hand, hypothesized that there are two cell lineages with different functions in adaptive immunity and verified their existence through experiments on chickens. Their pioneering achievements laid the foundation for the next half century of developments in immunology from basic concepts to applied research. The development of new therapeutic drugs for cancers and immune disorders, which has been attracting much attention in recent years, would not have been possible without Dr. Cooper and Dr. Miller's discoveries.

"B and T lymphocytes", the key players in adaptive immunity

Living organisms have an ingenious defensive mechanism called "immunity" that provides defense against foreign invaders, such as pathogens, which threaten the body's normal functions and condition, thereby preventing the host from contracting epidemics. The immune system keeps a record of past invasions, so that it could respond immediately to defend the host in case of a recurring attack by the same pathogen.

A living body has two types of defense mechanisms: "natural immunity", which is innate to living organisms, and "adaptive (acquired) immunity", which is specifically triggered in response to foreign invaders that penetrate natural immunity's defense barrier.

When foreign invaders such as pathogens break through the epithelial barrier into the body of the host, natural immunity immediately responds by attacking the invader with a cell group consisting of macrophages, neutrophils and natural killer cells. A short time later, the more sophisticated adaptive immunity takes over. The main constituents involved here are the B lymphocytes (B cells) and T lymphocytes (T cells).

Up until the early 1960s, when Dr. Cooper and Dr. Miller began their research, interest among researchers was concentrated on antibodies. The central concern of immunology in the first half of the twentieth century was "humoral immunity", or immune phenomena involving antibodies.

In contrast to antibodies contained in the serum, or the liquid part of the blood, immune phenomena caused by lymphocytes contained in blood cells are called "cellular immunity". Since the 1940s, immune responses involving lymphocytes, separate from humoral immunity, gradually came to be better understood, and over time, facts suggesting the existence of two types of immunity were reported. However, not until Dr. Cooper and Dr. Miller reported their research results could the existence of the two types be confirmed and the cells involved identified.

Tlymphocytes were being produced by the mysterious organ, "the thymus"

After studying at the University of Sydney Medical School, Dr. Jacques Miller went to London in 1958 and began studying the pathogenesis of lymphocytic leukemia in mice at the University of London. At the time, Dr. Miller was strongly influenced by the leading immunologists, Dr. Peter Medawar and his pupil, Dr. James Gowans. Through experiments on rats, they discovered that lymphocytes play an important role in the rejection of grafts.

Lymphocytic leukemia in mice, which Dr. Miller was studying, develops and spreads from the thymus due to viral infection.

Having hypothesized that the thymus is where virus multiplication takes place, Dr. Miller decided to remove the thymus gland of a newborn mouse and see if injecting a virus would cause leukemia to develop. The treated mouse grew unexpectedly weak, and dissection revealed a reduction in lymphocytes in the lymph nodes and spleen.

Next, Dr. Miller transplanted a skin graft to the same mouse to see if it would be rejected. He knew from Prof. Medawar and Gowans' research that lymphocytes would normally cause the graft to be rejected. But to his surprise, Dr. Miller observed that the skin of a heterologous mouse was successfully engrafted on the mouse with its thymus removed.

Also, by marking the lymphocytes and observing their movement throughout the body, he confirmed that lymphocytes originate from the thymus, which was regarded as a mysterious organ at the time.

These experiments confirmed that the thymus is the organ that produces and delivers lymphocytes. When he reported this discovery in 1961, Dr. Miller named this lymphocyte the thymus-dependent lymphocyte, which later came to be known as the "T lymphocyte", with the T taken from the word, thymus.

In addition, Dr. Miller discovered that there are two types of lymphocytes with different functions, and that the thymus-dependent lymphocytes (T lymphocytes) are not only involved in immune responses that reject skin grafts, but also play a role in supporting the function of myeloid-dependent lymphocytes (B lymphocytes) responsible for the production of antibodies.

Demonstrating the two types of immune systems using chickens

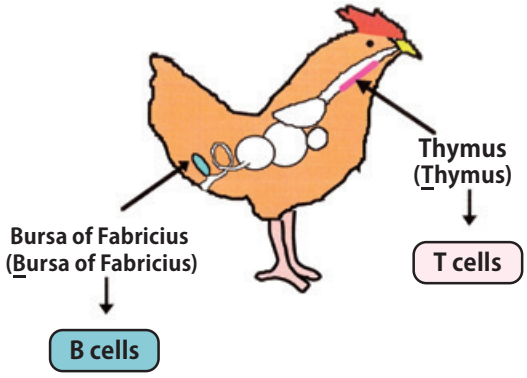
Dr. Max D. Cooper became a pediatrician after graduating from the Tulane University School of Medicine. From 1963, he conducted research at the University of Minnesota under Prof. Robert Good, a leading figure in immunology research. At the time, Dr. Cooper was fascinated by a report indicating the possibility that the bursa of Fabricius in chicken is involved in the production of antibodies. Follow-up studies by other researchers also suggested that the bursa of Fabricius is responsible for immune functions different to that of the thymus, but there was no conclusive evidence.

Meanwhile, Dr. Cooper, from his clinical experience as a pediatrician, found hints of the existence of the two types of immune systems. In a patient with a certain hereditary immunodeficiency disease, Dr. Cooper detected sufficient levels of antibodies despite an abnormal proliferation of herpesviruses. However, in the case of another hereditary immunodeficiency disease, the patient was highly resistant to viral infection although no antibody response could be observed. From these cases, Dr. Cooper hypothesized that there are two types of adaptive immunity: one in which antibodies are involved and one in which it is not.

To confirm the role of the bursa of Fabricius and the thymus, as well as the existence of the two types of adaptive immunity, Dr. Cooper conducted the following experiment.

Newborn chickens whose bursa of Fabricius or thymus had been removed were irradiated with X rays to destroy any cells that may have been created before hatching. Their immune functions were then examined in detail. The results showed that the chicken whose bursa

Dr. Cooper's experimental results



	Antibody production	Rejection of skin grafts
Chicken with the bursa of Fabricius removed	↓↓	OK
Chicken with the thymus removed	Mostly OK	↓↓

Chickens with the bursa of Fabricius removed cannot produce antibodies. In chickens with the thymus removed, rejection of skin grafts do not occur. This experiment confirmed the existence of B lymphocytes responsible for antibody production and T lymphocytes responsible for rejection reactions.

of Fabricius had been removed had no antibodies, while the chicken whose thymus had been removed had lost the ability to reject skin grafts, just like the mouse with its thymus removed (see figure).

This experiment revealed that cells derived from the bursa of Fabricius are essential for antibody response, and that cells derived from the thymus are involved in the rejection of skin grafts. Thus, the existence of the B lymphocyte lineage responsible for humoral immunity and the T lymphocyte lineage responsible for cellular immunity was demonstrated. Cells derived from the bursa of Fabricius came to be called “B lymphocytes” with the B taken from the word, bursa. Thereafter, Dr. Cooper and his colleagues revealed that in humans, B lymphocytes are produced in the bone marrow, whose initial is also B.

Dr. Cooper further extended his findings to other animals through his discovery that the basic mechanism of controlling adaptive immunity by the two lymphocyte lineages is widely preserved in vertebrates, from humans to jawless species such as the lamprey, thereby deepening our understanding of the evolution of adaptive immunity.

Epoch-making contributions to modern immunology and to the treatment of intractable diseases and cancer

Dr. Cooper and Dr. Miller’s accomplishments established the basic concepts underlying modern immunology and served as the driving force behind the significant advances in immunology that followed. In addition to major advances in the understanding of the pathology of numerous immune disorders including autoimmune diseases, allergies and chronic inflammatory diseases, their concepts have also been adapted into many new therapeutic and diagnostic drugs. More recently, there has been grown anticipation surrounding the substantial progress being made in new epoch-making cancer treatments that utilize antibodies and immune cells, such as antibody drugs, immune checkpoint inhibitors and genetically modified T-cell therapies. These developments are manifestations of the power of modern immunology, of which the foundation was laid by Dr. Cooper and Dr. Miller’s pioneering research, and their legacy will continue to widely benefit society into the future.