

Immunotherapy Toward Autoimmune Disease and Cancer

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Abstract. Specific immunity refers to the ability of the human body to resist infection obtained by acquiring infection. It is generally formed after microbial and other antigenic material stimulation and the activation of lymphocyte and the production of immunoglobulin is typical of this process. If the specific immune response is not correctly triggered, some neoplastic diseases (such as cancer) may develop as the tumor cell can escape the immune response. If the specific immune response is wrongly triggered, autoimmune diseases may be developed as the immunoglobulin and active lymphocyte may accumulate against self-antigen on different somatic cell. The specific immune response inhibition in autoimmune response and arousal or manipulation of the specific immune response toward cancer (such as CAR-T cells therapy) has intrigued investigators recently. In this article, the causes, treatments and possible further researches for autoimmune disease are presented and mechanism of immune escape, as well as modern treatment, especially CAR-T cells for tumour are included for future research.

1 Introduction

Since Donath and Landsteiner proposed this concept, Many diseases are classified as autoimmune. However, the existence of autoantibodies is a different concept from autoimmune disease. Autoantibodies can exist in normal people without autoimmune diseases, such as anti-thyroglobulin, thyroid epithelial cells, gastric parietal cells, nuclear DNA antibodies, etc.

Causes of autoimmune disease (the relationship with immune system and immune response)

Tumor cells, in order to survive and grow in the face of the body's immune system, employ several strategies to "escape."

There are two main strategies as follows:

(1.) "Camouflage," in which tumor cells block T cell from receiving tumor antigens on the surface of tumor cells, causing T cells to mistake tumor cells for normal cells. By disguising themselves as normal cells, they escape the T cells.

(2.) "Vertigo", after tumor cells are recognized by T cells, it prevents T cells from secreting antibodies that can kill tumor cells normally, and induces T cells to gradually enter death.

Therefore, in order to restore the body's own immunity to tumor cells, scientists have conducted a lot of exploration, and successfully found a number of tumor immune escape pathways, among which the PD-1/PD-L1 pathway is the most experienced one.

Pd-1 is a protein on T cells and an important immunosuppressive molecule. The expression of PD-1 can induce

T cell death, thereby preventing the occurrence of autoimmunity. But PD-1 is not expressed without binding to the corresponding ligand. Pd-l1 is a ligand of PD-1, which exists in many tissues. Currently, it has been found that many tumor cells also express PD-L1. Pd-l1 on tumor cells can precisely combine with PD-1 on T cells, leading to the expression of PD-1, thereby inducing the death of T cells and eventually making the human autoimmune system have no response to tumor cells [1]. It's not that our immune system itself can't kill tumor cells. It's that wily tumor cells have evolved to learn how to evade our immune system. In order to fight against cunning tumors, in addition to directly killing tumors by means of radiotherapy and chemotherapy, it is also an important means to restore the recognition and killing of tumor cells by our immune system. Pd-1 inhibitors, which have been approved for marketing in the United States, can restore the recognition and killing ability of the human immune system to tumor cells. It can specifically bind to PD-1 on T cells and put a "gas mask" on PD-1 to inhibit the expression of PD-1 and resist PD-L1 of tumor cells. Thus, the function of inhibited T cells can recover the recognition function of tumor cells and achieve the effect of anti-tumor.

However, now there is a new treatment for these diseases—CAR T Cells Therapy. Car-t therapy involves collecting and isolating T cells from a patient's blood, and then genetically modifying them to enhance their ability to target and kill cancer cells. The T cells are cultured and expanded in large quantities in vitro, then injected into the patient, where they continue to multiply, and eventually recognize and destroy cancer cells in the body. Car-t therapies are more lethal to tumor cells, more targeted, and

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longer lasting. Each CAR-T is specifically designed to target the surface antigens of the tumor in the patient's body. Experiments have shown that these genetically modified T cells can still exert anti-tumor activity when cancer cells reignite in the body [2].

2 Background and State of the Art

The importance of T cells is well illustrated by the fact that there are about 300 billion T cells in the body of an adult. Morphologically, T cells are so similar to B cells, in fact, even immunologists can't tell them apart under an ordinary microscope. Like B cells, T cells are produced in the bone marrow and have antibody-like molecules on their surfaces called T cell receptors (TCR). Like the BCR on the surface of B cells, the TCR is formed through a strategy of mix-and-match and combinatorial design. So TCR is as diverse as BCR. At the same time, T cells also follow the principle of clonal selection: when the receptor of a T cell binds to its homologous antigen, the T cell can proliferate to form a T cell clone with the same antigen specificity. This process takes about a week to complete, so like antibody responses, T-cell responses are slow and specific. Although there are many similarities between T cells and B cells, there are also some important differences. For instance, B cells are mature in bone marrow, while T cells mature in Thymus. In addition, B cells produce antibodies that can be recognized by any organic molecule, while T cells recognize only protein antigens. Moreover, B cells can release their receptors in the form of antibodies, while T cell receptors stick to the cell surface. Most importantly, a B cell can recognize antigens on its own, while a T cell is more like an English gentleman, recognizing only those antigens that are presented to it by other cells.

T helper cells are a type of white blood cell that has antigen receptors on their surfaces that recognize antigen fragments presented by the antigen-presenting cell's MHC Class II molecule. As for the mode of action, in general, the role of T helper cells in assisting B cells to form antibodies is to concentrate and concentrate antigens, which may be in two ways:

(1.) Direct carrier concentration in T cell antigen recognition, B cells to identify hapten, formed between the two antigens bridge the B cells and T cells together, which is advantageous to the antigen receptors decided to B cells in a cluster, the cell can reach the signals produced by B cells and cause B fine run activation, and then into antibody-forming cells and antibodies. This mode of action is the interaction mode of linkage recognition.

(2.) Indirect concentration of antigen T helper cells to assist B cells acts through non-specific mediators or lymphokines produced by T cells. Nonspecific mediators are produced and released in response to the stimulation of antigens, allo-antigens or mitogens. They are also called T cytokines because they are produced by cells. There may be multiple types of T cytokines, and not all of them act in the same way. Some have strong affinity with macrophages and can bind to the surface of macrophages, and then the macrophages will bring the antigen to B cells and bind to the hapten part of the antigen. This also indirectly

acts as a concentration of antigen. This mode of action is polyclonal interaction [3]

On the other hand, T Killer cells recognize and kill those cells that are infected by the virus. Killer T cells destroy these virus-infected cells by making contact with specific target cells and initiating their "suicide program." This method is an effective way to kill the virus that has already infected the cell, when the infected cell dies, so does the virus inside the cell [3].

Autoimmune diseases can be divided into two main groups:

(1.) Organ-specific autoimmune diseases:

Pathological damage and dysfunction of tissues and organs are limited to the specific organ targeted by antibodies or sensitized lymphocytes. There are mainly chronic lymphoid thyroiditis, hyperthyroidism, type 1 diabetes mellitus, myasthenia gravis, chronic ulcerative colitis, pernicious anemia with chronic atrophic gastritis, pulmonary haemorrhage nephritis syndrome, pemphigus vulgaris, pemphigoid, primary biliary cirrhosis, multiple cerebrospinal sclerosis, acute idiopathic polyneuritis, etc. The common ones will be described in each system disease.

(2.) Systemic autoimmune diseases:

Due to the extensive deposition of antigen-antibody complexes in the blood vessel wall and other reasons, it leads to the damage of multiple organs in the whole body, which is called systemic autoobligh. Commonly referred to as collagenopathy or connective tissue disease, it is caused by immune damage leading to cellular-like necrotizing inflammation of the vessel wall and interstitium and subsequent proliferation of multiorgan collagen fibers. In fact, most collagen fibers have no primary changes in ultrastructure and biochemical metabolism [4].

Specific immune response formation process (cancer):

Under antigen stimulation, the specific immune response of the body can be divided into three stages: induction, response and effect. It is divided into three stages:

(1.) Induction stage is the stage of antigen processing, presentation and recognition;

(2.) The reaction stage is the stage of B cell, T cell proliferation and differentiation, and the formation of memory cells;

(3.) Effector stage is the stage when effector T cells, antibodies and lymphokines exert immune effects.

If certain pathogens break through the first and second lines of defense, that is, enter the body and grow and multiply, causing infection. Some have symptoms, is the disease; Some have no symptoms and are called silent infections. No matter which kind of case, the body has experienced a process of fighting against the pathogen. This kind of recognition and killing action, specifically against a certain pathogen (antigen) is called specific immunity. For example, people who have had typhoid fever have long-lasting immunity to Typhi because typhi stimulates an immune response, increases the phagocytosis of macrophages, and produces antibodies against Typhi in the body. The immune system of the human body can "remember" the characteristics of the "enemy" Typhi Bacillus for a long time. If another Typhi Bacillus enters, it will be quickly recognized and destroyed. There are many types of immune cells that can provide an immune response, the

most important being lymphocytes. It falls into two categories. The two types of cells develop and mature differently, one is in the thymus, called T lymphocytes, and the other is in the bone marrow, called B lymphocytes.

Macrophages with the ability to swallow foreign bodies are also important immune cell, which plays the role of "processing plant", that means, after phagocytosis of foreign bodies (such as bacteria, tumor cells, etc.), macrophages process foreign bodies. The treated foreign body (antigen) initiates an immune response with T and B lymphocytes and can kill the foreign body directly or produce cytokines involved in the immune response.

After being stimulated by pathogens, B lymphocytes cause a series of changes and eventually transform into plasma cells that can produce antibodies. The antibodies produced can destroy pathogens by various means, such as lysis of pathogens, neutralizing toxins produced by pathogens, agglutinating pathogens into larger particles for swallowing and elimination by phagocytes. The antibody that plasma cell produces exists in the blood of airframe and humoral fluid, this kind of immune response calls humoral immunity.

When the treated pathogen stimulates T lymphocytes, it also causes a series of changes that eventually transform them into sensitized lymphocytes that release lymphokines. There are many types of lymphokines with different roles, and they actively participate in the immune response, which is often called cellular immunity. Humoral immunity and cellular immunity are not isolated. They complement each other and cooperate with each other to play the role of immunity together.

Treatment mechanism [5]:

(1.) Regulatory T cells regulate the function of T helper cell subsets (Th1/Th2);

(2.) "Blocking antibody" theory: This theory holds that IgG can competitively block the binding of allergen to IgE on mast cells, thereby avoiding mast cell activation and release of inflammatory mediators;

(3.) Regulation of IgE;

(4.) Inhibition of effector cells and inflammatory response;

(5.) modified dendritic cells (DC) to induce immune tolerance;

(6.) Induction of peripheral tolerance, that is, IL-10-induced antigen-specific T cell inactivation can form peripheral tolerance;

(7.) Regulatory effect of regulatory T cells (CD4+CD25+Tr cells) [6].

The mechanisms of SIT are complex, and the mechanisms of immunotherapy vary according to the nature of the allergen, the tissues and organs involved in the disease, the method, dose and duration of immunotherapy, the type of adjuvant used, and the heritability of the individual. Therefore, elucidation of the mechanism is of great significance to improve the clinical efficacy and safety of SIT.

Specific immunity prevention and treatment:

Specific immunity can be obtained by disease, recessive infection, vaccination, injection of antitoxin and so on.

Methods of immunity acquisition:

"Active Immunization"

(1.) Natural active immunity: disease, recessive infection.

Artificial active immunization; 3. Inoculate vaccine, toxoid, etc.

"Passive Immunity"

(1.) Natural passive immunity: through the placenta, colostrum.

(2.) Artificial passive immunization; 3. Injection of antitoxin, gamma globulin, cytokines, etc.

Artificial immunity is to use artificial methods, such as vaccine, toxoid or contain some specific antibody, cell immune preparation and other inoculum in the human body, in order to enhance the body's resistance to disease.

Biological products immunogen (vaccine, toxoid, etc.), immune sera, cellular immune preparations, diagnostic preparations (tuberculin, diagnostic serum, diagnostic antigens, etc.) and other biological preparations used in artificial immunization are collectively referred to as biological products [5],

3 Future Direction

Rates of autoimmune diseases such as multiple sclerosis and type 1 diabetes have soared in developed countries in recent decades. In the three new studies, scientists expanded their understanding of how a type of immune cell called helper T cell 17(Th17) is formed and how its growth affects immune responses. By elucidating these cellular association mechanisms, researchers have uncovered a surprising link between salt intake and autoimmunity, highlighting the interplay of genetic and environmental factors in disease susceptibility.

The human immune system is in a delicate balance: too little activity can leave an individual vulnerable to foreign invaders, while too much activity can harm the organism that is supposed to be protected. When this delicate balance is disrupted, autoimmune diseases can result. But little is known about the molecular circuits that maintain this delicate balance.

Th17 cells can promote inflammation and play an important role in the defense against pathogens, but they are also associated with many diseases, including multiple sclerosis, psoriasis, rheumatoid arthritis and coercive spondylitis. Manipulating the function of T cells has become the treatment of choice for some of these diseases [4].

Currently, CAR-T cell-related clinical studies have shown that CAR-T cell therapy can cure some cancers. These cancer patients were able to achieve complete remission after receiving CAR-T cell therapy. Studies have found that CAR-T cell therapy leads to a significantly better complete response rate for advanced cancer than conventional therapy. Car-t cell therapy was first shown to be effective in a subset of patients with non-Hodgkin's lymphoma.

Through continuous improvement, it has been approved for clinical treatment. Basically, CAR-T cell technology uses gene transfer technology to transfer constructed CAR receptors to immune effector cells to target tumor cell killing [7]. However, this therapy has not been widely used in clinical practice, on the one hand, because the preparation procedure of CAR T cells is complex and

the technical threshold is high. On the other hand, the efficacy of CAR T cells in solid tumors is not satisfactory. Numerous clinical trials of CAR T cells in solid tumors are being carried out, hoping to create more efficient CAR T cells through various technologies to seek breakthroughs in solid tumors. The good news is that the recent approval of the first CAR-T drug for relapsed and refractory diffuse large B-cell lymphoma in China may further promote the clinical application of CAR-T therapy [2]. From my personal perspective, since it is a virus that imbues the CAR-T gene into bloodstream, it is important to select the type of virus as the vector carefully, not the type of virus that can easily stimulate the immune system and have high side effects.

4 Conclusion

In this article, we talk about some of the most important cells that make up the immune system and how they work to protect our body health. It also mentioned some novel cancer therapies, such as Car-T cells therapy. In AACR's outlook for cancer treatment, precision immunotherapy has become the focus of 2022. In recent years, individualized treatment has been developed to determine which treatment options to give to patients based on their individual tumor characteristics. These features mainly include protein markers and DNA mutations expressed by tumor cells. A precise understanding of tumor characteristics can predict which patients will respond to immunotherapy.

A typical example is the use of immune checkpoint inhibitor (ICB) therapy to predict which patients are likely to be sensitive to immunotherapy by tumor characteristics such as PD-L1, TMB, dMMR, and MSI. CAR T cells, which are harvested from patients, have been genetically engineered to be tumor-targeted, more patient-specific cellular immunotherapy. These two types of therapies are a milestone breakthrough in tumor immunotherapy in the past 10 years, and also one of the complementary examples in the field of precision medicine and immunotherapy in recent years [8].

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