

Mechanisms of Autoimmunity

—Recent concept—

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Abstract: Autoantibodies and autoreactive T cells, which exist even in healthy individuals, are usually regulated by a mechanism called immunological tolerance. For example, peripheral T cells are subject to various types of regulatory mechanisms, including clonal deletion, anergy, clonal ignorance, and T cells with regulatory functions. It is believed that autoimmune response may initiate when such regulated immune responses are pathologically activated by a certain trigger, probably a limited antigenic stimulation. Thereafter, other factors that promote autoimmune responses combine to develop an autoimmune disease. It is estimated that T cells are closely involved in these reactions.

Key words: Immunological tolerance; Molecular mimicry; Epitope spreading

Introduction

Autoimmunity is generally defined as a phenomenon in which antibodies or T cells react with autoantigens. Autoimmunity induces autoimmune diseases. Recent studies have revealed that such autoantibodies or autoreactive T cells exist even in healthy individuals. The immune system has various mechanisms to suppress the immune response to the self, and the disturbance of these mechanisms results in autoimmune diseases.

Autoimmunity and Autoimmune Diseases

The conventional clonal deletion theory

assumes that the immune system definitely distinguishes between self and non-self, and that autoreactive B and T cell clones are eliminated before they mature. However, recent studies have demonstrated that this theory, although basically correct, does not always hold true. B and T cells that react with autoantigens exist in the peripheral blood of healthy individuals.

For example, T cells that react with autoantigens, such as myelin basic protein (MBP) of myelin sheath and type II collagen of cartilage, can be separated from the peripheral blood of healthy individuals. Furthermore, autoimmune diseases such as thyroiditis can be induced in normal animals by immunizing them with organ-specific antigens such as thyro-

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globulin, indicating that lymphocytes that react with the autoantigens exist in normal animals. Therefore, it is believed that the existence of autoantibodies or autoreactive T cells is not enough to elicit autoimmune diseases. In addition, it has been recently speculated that auto-reactivity at a low level is physiological and necessary for a normal immune response. It has been reported that the weak reactivity to autoantigens presented by major histocompatibility complexes (MHC; for humans, HLA) might be necessary for the survival of peripheral mature T cells and maintenance of homeostasis.

Considering these factors, it is important to distinguish specific autoimmune responses that cause various autoimmune diseases from the existence of autoreactive lymphocytes or simple autoimmune response. For example, injection of spermatozoa into an animal results only in the production of autoantibodies against spermatozoa, but it does not cause any disease. However, the immunization of an animal with spermatozoa mixed with an adjuvant that strongly stimulates an immune response results in autoimmune testitis. Therefore, autoimmune diseases are distinguished from mere autoimmune response not by the presence/absence of autoimmune response, but by the different quality and quantity of the autoimmune response.

Autoimmune diseases are divided into two groups: the organ-specific autoimmune diseases, in which the target antigens and the tissue disorders are localized in one organ, and the systemic autoimmune diseases, in which the response to a certain type of antigens that are expressed widely in the body, such as an intranuclear antigen and multiple organs are involved. There are several autoimmune diseases that stand between these two groups. It remains unclear whether these two groups of autoimmune diseases result from the same or substantially different mechanisms.

Mechanisms of Immunological Tolerance

Immunological tolerance is defined as a state in which the immune system does not positively respond to autoantigens. The concept of immunological tolerance for autoreactive T and B cells has been changing rapidly as new experimental systems have been established.

T cells, which play a central role in acquired immunity, undergo clonal deletion by apoptosis when they are exposed to a sufficient amount of autoantigens in the thymus where they differentiate. This is called central tolerance. It has been revealed recently that some molecules previously considered to be expressed only in a specific organ are also expressed in medullary epithelial cells of the thymus. This indicates that the thymus is intended to express as many autoantigens as possible in the body to induce tolerance for them. However, this mechanism is limited by the fact that not all autoantigens are expressed in the thymus. Furthermore, T cells that weakly react with autoantigens can migrate into peripheral tissue. Each antigen should have multiple amino acid sequences that can bind to antigen-presenting MHC molecules. These sequences are called epitopes or antigenic determinants. However, some epitopes are not presented as antigens under usual conditions probably due to the relationship with other epitopes or proteolysis in the cells. Such epitopes are called "cryptic epitopes," which means hidden antigenic determinants. T cells cannot become tolerant to them.¹⁾

T cells that migrate into peripheral tissues undergo clonal deletion by apoptosis in the similar way as in the thymus when the stimulus of autoantigens is strong. When the stimulus is not strong enough, T cells undergo clonal anergy (clonal paralysis). When the amount of autoantigens is further reduced, T cells become ignorant (non-tolerant and unresponsive). In this regard, it is important that naïve T cells circulate only in lymphoid organs without

entering other organs to maintain the state of ignorant.

It has also been reported that tolerance may be actively suppressed by regulatory T cells. Recent studies have reported T cells with various regulatory functions, including those that produce cytokines with suppressive effects, such as interleukin (IL)-10 and transforming growth factor (TGF)- β , and those that have CD4+ and CD25+ surface markers and provide suppressive effect through cell-cell contact. These various suppressive T cells may play different roles, depending on the activation of autoreactive T cells.

Thus, autoreactive T cells are under substantially different conditions of tolerance, depending on the quality and quantity of autoantigens. For example, many autoantigens are too isolated from the immune system to activate potential autoreactive T cells. Autoantigens expressed on non-hematopoietic cells may not stimulate T cells because they do not have co-stimulatory molecules. Another mechanism has also been revealed in which the lymph nodes around organs have dendritic cells that take antigens to induce tolerance of autoreactive T cells in the steady state condition.

B cells have been reported to undergo anergy in response to soluble autoantigens and clonal deletion in response to stronger autoantigens, such as those on cell surfaces in the bone marrow where they differentiate. B cells that strongly react with soluble antigens such as self-molecules at the germinal center of peripheral tissues are also deleted through apoptosis. B cells have been reported to cause a phenomenon called receptor editing in which B cells that react with an autoantigen rearrange the gene of the antigen receptor (immunoglobulin) once again to make another non-autoreactive receptor.

Mechanism of Initiation of Autoimmunity

It is generally believed that autoimmunity is

triggered by the development or activation of CD4+ helper T cells that react with a specific autoantigen. Based on various evidence, it is now proposed that a specific antigenic stimulus is the first trigger of autoimmunity. This is called the “single initiating antigen hypothesis”.²⁾ For example, molecular mimicry in which immune response occurs to both an external microbial antigen and an autoantigen because of their homology is considered one of the mechanisms of initiating autoimmunity.

Microbial infection may initiate autoimmune response not only through molecular mimicry, but also with polyclonal activation and release of isolated autoantigen. Lipopolysaccharide (LPS), a product of infectious microbes, bacterial DNA, and viruses serve as an adjuvant to immune response. They bind to Toll-like receptors (TLRs) on the surface of macrophages or dendritic cells to stimulate natural immunity and inflammatory cytokine production, enhancing immune response by increasing the expression of MHC antigen or co-stimulatory molecules, such as B7-2 and OX40L. These responses are usually helpful for inducing acquired immunity, but may stimulate potential autoreactive T cells. Through these processes, it is also possible that cryptic epitopes not expressed under usual conditions are expressed to trigger an autoimmune response.

Non-infectious factors are also considered as a trigger of autoimmunity. For example, estrogen exacerbates systemic lupus erythematosus (SLE) in a mouse model, while drugs, such as procaine amide and hydralazine, induce the production of antinuclear antibodies, causing an SLE-like pathologic state. The amount of iodine intake is an important environmental factor in autoimmune thyroid disease.

Mechanisms of Development of Autoimmune Diseases

Triggering autoimmunity alone probably results in a transient event and is insufficient to induce autoimmune disease. Studies in mouse

models have shown that CD4+ T cells may be required to complete the pathological state of most autoimmune diseases. Animal experiments have demonstrated that the onset of autoimmune diseases can be suppressed by removing or inhibiting the function of CD4 cells with anti-CD4 monoclonal antibodies. Furthermore, the importance of antigen-specific CD4 cells in pathological autoimmune condition has been suggested from the association with MHC class II antigens (such as DR antigen of HLA in humans), infiltration of CD4+ cells in many organ-specific autoimmune diseases, and production of autoantibodies of IgG type.

Although various factors are associated with the progression of autoimmune diseases, one of the important phenomena is epitope spreading. Epitope spreading refers to a phenomenon in which autoantigens (antigen determinants) detected by T and B cells increase during the process from the initial activation of autoreactive lymphocytes to the chronic phase. This concept is important for explaining, for example, the mechanism by which autoimmune response induced by one cryptic epitope leads to complete autoimmune response. Both B and T cells are involved in this phenomenon. Particularly, B cells play an important role as antigen-presenting cells for T cells.

In contrast, a study using non-obese diabetic (NOD) mice as a type I diabetes model showed that autoimmune disease may progress through the avidity maturation and selective expansion of a particular antigen-specific T cell clone. We

have also shown from the analyses of T cell clonality infiltrating into organs that reactive epitope is not always spread during the progress of a disease. Probably, such positive and negative balance of immune responses with regard to reactive epitopes may be involved in the persistence and progression of autoimmune diseases.

Conclusions

Autoimmune disease is generated through the disturbance of immunological tolerance. Activation of autoreactive lymphocytes, and various positive and negative immune responses are involved in each of these processes. Genetically, individuals with lower threshold to these responses are more susceptible to autoimmune disease, although various environmental factors that induce such immune responses are also significant. It is thus necessary to understand in detail autoimmune phenomena in each patient to establish a proper therapy that suppress pathological immune responses without affecting normal immune functions.

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