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Autoimmune Processes, Development Mechanisms, Biological Bases

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Abstract: The article analyzes the possible mechanisms of the development of autoimmune processes, the types, the importance of an infectious agent in the occurrence of an autoimmune process, about existing hypotheses and the influence of genetic factors on the pathogenesis of autoimmune diseases that develop as a result of the pathological production of autoimmune antibodies, which can be the causes of the occurrence of pathological processes of an autoimmune nature of various etiology.

Keywords:autoimmune diseases, autoimmunity, primary immunodeficiency, immunization, SLE, thyrotoxicosis

Autoimmune processes are a wide class of immune diseases, the pathogenesis of which is supposed to suppress the mechanisms of self-tolerance and the development of aggressive classes of autoimmune killer cells of the own body against normal cells of the body, as a result of which pathological processes develop [2, 4].

In the last century, P. Ehrlich studied the reasons for the lack of immunological reactions to the body's own antigens and formulated an axiomatic formula - fear of self-poisoning. In the 50s, the immunological nature of transplant rejection, the phenomenon of immunological tolerance were proved, and the first successes were obtained in the study of the nature of autoimmune diseases. Of particular importance is the clonal selection theory of F.M. Bernet, which proved the death of clones of lymphocytes that carry an antigen-recognizing receptor capable of binding to autoantigens [4]. Additional hypotheses indicate the blockade of autoreactive clones by various mechanisms that lead to the activation of autoantibodies, but the production of a small amount of autoantibodies remains, the clones of which, under certain conditions, can multiply and become the cause of an autoimmune disease. By its physiological nature, autoreactivity is part of the physiological process of maintaining the body's homeostasis. It is known that autoantibodies are involved in the processes of apoptosis, regeneration, and elimination of cellular debris that occurs after natural cell death or damage [3]. In healthy people, they are determined in small quantities, and take part in immunological processes. However, a genetic predisposition can be the cause of an autoimmune disease.

Organ-specific autoimmune diseases develop due to the destruction of the histohematological barriers of organs that are separate from the immune system. As a result, the immune system reacts to the unchanged antigens of these organs, producing antibodies and sensitized

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lymphocytes, and changes in the type of delayed-type hypersensitivity develop in the organs [3, 21].

In the development of organ-specific autoimmune diseases, the leading factors are violations in the system of immunobiological surveillance. Autoimmunization develops in relation to antigens of many organs and tissues, in which there are changes characteristic of hypersensitivity of both delayed and immediate types.

The immune system exercises strict control over the internal homeostasis of the body, the physiological correspondence of individual cells and systems, their interaction in providing the general process of vital activity, the leading link in which is the immunological effect of suppression - the prohibition of the reaction to "one's own" [6].

However, a change in the antigenic structure of tissues, their physiological or pathological degradation, violations of various links in the immune system, for example, the appearance of somatic mutations of immunocompetent cells, leads to the development of **autoimmunity** - the reaction of the immune system against its own tissues. The emergence of autoimmune processes can be mediated as a result of trauma, infectious or other disease, or directly associated with dysfunction of T-suppressors and the development of cytotoxic control of the immune system of antigens of its own tissues [8].

It should be noted that autoimmune control is a physiological property of the immune system, and therefore the so-called "normal antibodies" are always present in the blood in threshold titers that control cell renewal within physiological limits. This is due to the fact that the body's immune antibodies contain autoreactive T- and B-lymphocytes, the functions of which are autorecognition aimed at maintaining self-tolerance and maintaining antigenic homeostasis. Autoimmune diseases can be caused by cross-reacting antigens, where antibodies are produced against both autologous antigens and microbial determinants. So, streptococci have antigenic commonality with antigens of the myocardium, basement membranes of the renal glomeruli. On this basis, the pathogenesis of rheumatism, chronic nephritis, etc. is formed [1, 15].

As a result of the accumulation of drugs, some of its own tissues can acquire foreign antigenic properties of the drug, falling under the immunological control of the body. Non-eliminated macromolecules of "embryonic primordia" can be autoantigens. Autoimmune diseases are more common in women. With age, the incidence of autoimmune diseases increases. In the implementation of autoimmune diseases, primary diseases have a special place, which consist of a group of genetically heterogeneous immune disorders that affect individual elements of the innate and adaptive immune system [18]. Patients with primary immunodeficiency are more likely to develop not only recurrent infections, but also non-infectious complications such as inflammatory or granulomatous conditions, lymphoproliferative and solid malignancies, autoinflammatory disorders, and a wide range of autoimmune diseases. Mutations in one or more genes that play a fundamental role in immunoregulation and / or the immune tolerance network are responsible for primary immunodeficiencies. Various immunological abnormalities, along with a compensatory and overly persistent inflammatory response, lead to tissue damage and, ultimately, to the manifestation of organ-specific or systemic autoimmune diseases. Some forms of primary immunodeficiency disorders are characterized by many specific autoimmune phenomena [7, 17, 19,].

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Autophagy-related gene polymorphism is implicated in several autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, psoriasis, and multiple sclerosis. Numerous studies show that autophagy and proteins are also involved in immune regulation [23, 28, 36].

The effectiveness of the vaccine is based on whether the host's immune response against the antigen can elicit a memory T cell response over time. Although the reported side effects have so far been mostly temporary and acute, vaccines can induce an autoimmune response in the immune system. Adjuvants and infectious agents can exert their immunostimulatory effect through various functional activities encompassed by the adjuvant effect. These mechanisms are common to various adjuvant triggered conditions resulting in the adjuvant-induced autoimmune / inflammatory syndrome ASIA syndrome. There are several reports of cases of autoimmune diseases after vaccination, however, due to the limited number of cases, different classifications of symptoms and the long latency period of diseases, each attempt at epidemiological research has so far failed [37, 39].

Aging of the immune system in humans and animals is characterized by a decrease in both adaptive and innate immune responses. Aging is also associated with a condition of chronic inflammation and an increased likelihood of developing autoimmune diseases. Epigenetic changes in non-dividing and dividing cells, including immune cells, due to environmental factors contribute to inflammation and autoimmunity, which characterize both the condition and diseases of aging [22, 24, 51].

According to modern concepts, for the development of an autoimmune disease, in addition to a genetic predisposition, other environmental factors, microorganisms, persistent organic pollutants also affect. To date, the relationship between infectious processes and autoimmunity is being considered. In this problem, the role of hepatitis B and C viruses, herpes viruses, Coxsackie B viruses, S. pyogenes is being studied. Also, some authors have reported on the activation of autoantibodies in diseases of the human immunodeficiency virus. Questions about the trigger role of microorganisms and their enhancement of the subthreshold autoimmune response are discussed. There are several hypotheses about the significance of an infectious agent in the occurrence of an autoimmune process [11, 41].

One of the oldest is the hypothesis of "hidden" antigens or cryptantigens, barrier antigens of the organs of the thyroid follicles, testes, the internal environment of the eye, the brain, as well as intracellular proteins such as cardiomyosin, actin, toponin are "invisible" to lymphocytes. When exposed to microbial proteases, the histohematogenous barriers are disrupted and latent antigens are released, against which an autoreactive clone is activated, which can cause autoimmune disorders. But not every case gives rise to the synthesis of autoantibodies, despite the existing significantly small cases of the disease, the process of autoantigen presentation has not yet been fully elucidated [40, 50].

Expansion of the spectrum of epitopes can be considered as one of the components of the physiological response of the immune system to an infectious agent. The epitope is known to be recognized at the first contact; subsequently, cell immunity, specific for the epitope -T and -B, is activated. With repeated contacts with the pathogen, new antigen epitopes will be recognized in relation to which specific T-lymphocytes and antibodies are formed. Thus, effective immunological control is controlled, but the risk increases that some of the

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lymphocytes or antibodies will be able to react with their own antigens, that is, start the processes that ultimately lead to autoimmune disorders [25, 33, 35].

Another hypothesis is related to the modifications of antigens, according to which pathogens can modify the antigenic epitopes of the macroorganism's own tissues, converting them into autoantigens. The produced antibodies and cytotoxic lymphocytes bind both to modified autoantigens and to true autoantigens, in which an autoimmune disease can develop [9, 26].

Also plays a role of microorganisms in epigenomic changes. Some bacteria can disrupt the methylation of deoxyribonucleic acid in the DNA of the Toll-like receptor type 4 TLR4 of the host. Hypomethylation of DNA increases the expression of many genes, including genes for proinflammatory cytokines, T-cell growth factors, adhesion molecules, and others, while normal antigen-specific T-lymphocytes are transformed into autoreactive cytotoxic cells. The level of DNA hypomethylation is increased in CD4 + lymphocytes in rheumatoid arthritis and systemic lupus erythematosus [10, 13].

Molecular mimicry. According to the hypothesis of molecular mimicry, microorganisms can escape from immunological surveillance, due to the homogeneity of the same surface proteins in structure with the cells of the macroorganism [49, 53]. K. Damian was the first to suggest this in the 60s of the last century. Currently, the theory of molecular mimicry has changed and is presented in two versions. According to the first version of the theory, some microorganisms do indeed have cross-reactivity with the antigenic determinants of the host, perhaps not due to identity, but due to a rather pronounced similarity. Indeed, the primary role of the immune system is to protect the body from infections. For this purpose, the main cells of the immune system T- and B-lymphocytes are equipped with antigen-recognizing receptors of very different specificity, which allows them to recognize any infectious agent that has invaded the body [12]. Having recognized a foreign agent, the immune system is protected by the production of humoral antibodies, the generation of cytotoxic T-lymphocytes. In the first defense mechanism, antibodies infect extracellular infectious agents and their toxins, forming immune complexes, in the second mechanism, to save the whole body, cytotoxic T-lymphocytes have to destroy their own cells, in which intracellular pathogens are hidden. Thus, immunity to infectious agents quite often has an immunological component either in the form of immune complexes or in the form of cytotoxic T-lymphocytes. It follows that, developing an anti-infectious response, the immune system must "choose" the strength with which it defends itself: the response must be sufficient to eliminate the pathogen, but harmless to the body [20, 54].

According to the second version of the theory of molecular mimicry, the host's own antigens can be modified under the influence of various factors: prolonged exposure to infectious agents, the influence of free radicals, NO, xenobiotics, drugs, exposure to environmental factors, ionizing and ultraviolet radiation, exposure to low temperatures, etc. [55]. As a result of such influences, autoantigens are changed and recognized by the immune system as foreign (nonself-). The produced autoantibodies and cytotoxic lymphocytes bind not only to modified autoantigens, but also to true autoantigens due to the same cross-reactivity [27].

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The theory of the development of autoimmunity under the influence of superantigens. Bacterial superantigens got their name in connection with the ability to activate a large number of T- and B-lymphocytes, regardless of the antigenic specificity of these cells [45,52].

Activation of T-helper lymphocytes under the influence of superantigens nonspecifically binds to the variable part of the beta-chain of the T-cell recognition receptor outside its antigen-specific site. There is a kind of cross-linking of the molecules of the main histocompatibility complex of the antigen-presenting cell with the T-cell recognition receptor. Superantigen is able to stimulate 103 × 104 times more lymphocytes than processed antigen; allogeneic (foreign) superantigen can stimulate both helper (CD4 +) and killer (CD8 +) T-lymphocytes; autologous (self) superantigen can stimulate only T-helper lymphocytes (CD4 +); For full stimulation of T-lymphocytes with a foreign superantigen, an additional, costimulating signal is required [5, 14].

Three possible mechanisms of the participation of superantigens in the development of autoimmune disorders are considered. Activation of autoreactive T-lymphocytes. It has been proven that superatigens can directly activate autoreactive T-lymphocytes, which then migrate to the corresponding tissues and cause autoimmune disorders by producing cytokines and / or realizing their killing function. The activation of autoreactive B-lymphocytes is carried out due to the fact that the superantigen binds the molecules of the HLA class II complex, which are present on the B-lymphocytes, with the molecule of the T-cell antigen-recognizing receptor. In this case, the activation of T-lymphocytes occurs without specific recognition of the antigen, but nonspecifically under the influence of the superantigen. Nevertheless, such a T-lymphocyte produces the corresponding cytokines, which contribute to the fact that the activated autoreactive B-lymphocyte begins to produce autoantibodies. The latter form immune complexes and, settling in tissues, cause their damage. It is possible that B-lymphocytes can be activated through their own antigen-recognizing immunoglobulin receptor. Activation of antigen-presenting cells.Superantigens can activate antigen-presenting cells such as macrophages. This leads to the release of cytokines, superoxide anions and other inflammatory mediators from them. Activation of macrophages can also lead to impaired digestion of antigens with subsequent presentation of autoantigens to autoreactive T-lymphocytes [19, 30].

Adjuvant effect, or nonspecific (bystander) effect. According to another hypothesis, autoimmune diseases arise due to the fact that microorganisms activate receptors of innate immunity cells and / or induce the formation of pro-inflammatory cytokines, T-cell growth factors, and this, in turn, can lead to the activation and expansion of preexisting autoreactive clones of lymphocytes [34]. In part, this hypothesis overlaps with the hypothesis of "hidden" antigens, since both suggest that in the event of tissue damage and cell death, which inevitably occurs during an inflammatory response to a pathogen, self antigens become available to immunocompetent cells, including autoreactive ones. However, the main emphasis is placed on the fact that for the development of a pathological reaction to its own antigen, a second signal is required, which can arise due to nonspecific activation of APC during an infectious-inflammatory reaction. In other words, all cellular and humoral factors associated with a local inflammatory response to a pathogen can unwittingly contribute to the

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development of autoimmune responses according to the domino principle. Most often, this mechanism is associated with persistent viral infection, especially with the Epstein – Barr virus [43]. This hypothesis explains the need for the introduction of adjuvants in experimental models of autoimmune diseases. It has been established that a number of such adjuvants, for example, pertussin, stimulate TLR4 and inflammasomes, which in turn leads to the activation of Th1 and Th17 lymphocytes, which, according to modern views, are of key importance in the development of autoimmune pathology. Perhaps, with the simultaneous activation of innate immunity receptors by microorganisms and their own proteins, a synergistic effect occurs, leading to a breakdown of immunological tolerance and the development of autoimmune pathology [31, 60].

Antigenic complementarity. This hypothesis combines the main provisions of the hypotheses of molecular mimicry and idiotype-anti-idiotypic interactions. It is believed that a specific combination of microbial peptides may become the impetus for an autoimmune disease, and at least one of them should have similarities with their own antigens. Then, in response to the formation of primary antibodies directed against this peptide, anti-idiotypic antibodies will be produced [46]. As a result, the immune system ceases to recognize "self" and "alien" and produces autoantibodies, which, in a certain situation, can cause autoimmune pathology. Unlike the previous one, this hypothesis explains the adjuvant effect not by the influence of nonspecific inflammatory factors, but by the molecular complementarity of the antigen and the adjuvant. In this pair, each is an adjuvant in relation to each other, and this enhances the immune response that develops in each of them. Such hyperactivation leads to a complex deregulation of immune interactions and further to autoimmune disorders. If the adjuvant is not complementary to this antigen, then, despite the development of the immune response, autoimmune disease does not occur [42, 61].

Genetic factors. Autoimmune diseases in general are complex genetic diseases in which genes and the environment interact in unknown ways. It is important to emphasize that hereditary predisposition is inherent in all autoimmune diseases to varying degrees. In most cases, AID are polygenic diseases with incomplete penetrance, i.e. external causes influence their occurrence [57]. Thus, in identical twins, the concordance of the development of type 1 diabetes mellitus is 30–70%. In 10% of patients with rheumatoid arthritis, the disease has a close relative.

The predisposition to autoimmune diseases is associated with certain HLA haplotypes. HLA-B8 haplotype is found in many patients [56, 59].

Further evidence for the role of genetic factors in autoimmune diseases is the association of such disorders with certain HLA haplotypes. Thus, rheumatoid arthritis is not associated with the haplotypes of the HLA-A and HLA-B loci, but more often develops in the presence of a nucleotide sequence common to DR1 and the main DR4 subtypes. This sequence is also present in the heat shock proteins dnaJ of various bacteria and the gp 110 protein of the Epstein-Barr virus, which creates a clinically significant opportunity for the induction of autoimmune diseases by cross-reactive microbial epitopes [48]. Moreover, HLA-DR molecules carrying this sequence can bind another bacterial heat shock protein, dnaK, as well as its human analogue, the heat shock protein hsp73, which directs individual proteins to

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lysosomes where antigens are processed. In organ-specific diseases, haplotype B8, DR3 is especially common, although Hashimoto's thyroiditis is more often associated with DR5. It should be noted that DQ2 / 8 heterozygotes have a sharply increased risk of developing insulin-dependent diabetes mellitus. This confirms the idea of the participation of several genetic factors in the development of autoimmune diseases: firstly, genes that determine a general predisposition to autoimmune pathology, organ-specific or organ-specific, and secondly, other genes that determine a specific target of an antigen or antigens against which it is directed and autoimmune reaction [58].

Since the HLA gene products in the immune system present antigenic peptides to T cells, the set of HLA genes determines the direction of the immune response. Congenital presentation of foreign antigens leads to autoimmune reactions. HLA alleles are distinguished, which predispose to the development of one or another autoimmune disease, as well as HLA alleles, in the presence of which the likelihood of developing an autoimmune disease is low - the so-called "protective" alleles. Most autoimmune diseases are associated with the presence of the following antigens in the HLA phenotype: DR2, DR3, DR4, DR5. Rheumatoid arthritis is associated with HLADR4, Hashimoto's thyroiditis is associated with HLA-DR5, multiple sclerosis is associated with HLA-DR2, and systemic lupus erythematosus is associated with HLA-DR3. Associations with the MHC complex do not exhaust the links between the development of autoimmune diseases with certain genes. For example, the incidence of rheumatoid arthritis is associated with the HLA-DRB1 and HLA-DRB4 alleles, while the development of this disease is linked to the genes PTPN22 encodes intracellular tyrosine phosphatase 22, CIITA determines the expression level of MHC-II molecules, and PAD14 encodes peptidylargic protein 4 replacing arginine with citrulline. The PTPN22 gene is also associated with autoimmune damage to the thyroid gland [56]. In humans and mice, about 20 genes linked to the incidence of type I diabetes mellitus have been identified. Among these genes are CTLA4, IL2, IL1, IL4, TCRA, TCRB, Ins, etc. Described are polymorphisms of other genes of the immune system, which are often observed in autoimmune diseases. These include a number of cytokine genes, receptor molecules, congenital defects in complement factors, selective IgA deficiency

In addition to genetic factors, endocrine factors and gender play a large role in susceptibility to autoimmune diseases. It has been established that women are more susceptible to autoimmune diseases than men. So, the incidence among women of multiple sclerosis, rheumatoid arthritis is three times higher than in men, systemic lupus erythematosus nine times. It has also been noticed that some autoimmune diseases in women are more severe than in men [38,47].

Autoimmune diseases can be familial. The results of studies on single and fraternal twins, as well as data on the association of thyroid autoantibodies with X-chromosomal aberrations, convince that it is genetic factors that are the basis of familial cases, and not the influence of the environment. Familial autoimmune diseases are most often organ-specific [44, 47]. In this case, genetic factors determine not only the general predisposition to the appearance of organ-specific antibodies, but also the organ against whose tissue components they are predominantly directed. It is characteristic that in relatives of patients with Hashimoto's thyroiditis or pernicious anemia, the detection rate and titers of thyroid autoantibodies are higher than normal, and in relatives of patients with pernicious anemia, autoantibodies to

stomach tissue components are much more often present. Thus, there are genetic factors that determine the selectivity of gastric lesions in this group of organ-specific autoimmune diseases [16, 29, 32].

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