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DYSFUNCTION OF IMMUNE RESPONSE REGULATION AS A FUNDAMENTAL CAUSE OF AUTOIMMUNITY ONSET

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Aim. To investigate the types of immune response regulation and immunological tolerance disorders in autoimmune diseases.

Methods. Bibliometric indicators` analysis of scientific articles and analytical materials from databases such as Scopus, Web of Science, DOAJ, and PubMed were used.

Results. The most important types of regulation of the immune response, which are disturbed in autoimmune diseases, are the withdrawal of immunological tolerance to self-antigens (in which cellular and cytokine types of regulation become unbalanced) and genetic type. It analyzed the consequences of dysregulation of cellular, cytokine, genetic, idiotypic-anti-idiotypic, and immune-neuroendocrine types, which cause a breakage of immunological tolerance and the start of autoaggression.

Conclusions. The consequences of dysregulation of the immune response, which causes the reversal of immunological tolerance, create the ground on which numerous autoimmune reactions quickly form into an autoimmune syndrome and become autoimmune diseases.

Key words: immune response, immunological tolerance, Tregs, autoreactive B cells, apoptotic cells.

Regulation of the immune response is maintaining a balance between stimulation and suppression of immune processes. There are many types of immune response regulation, the most well-known being cellular, cytokine, genetic, idiotype-anti-idiotypic, and immuno-neuro-endocrine regulation. The most important types of immune response regulation disrupted in autoimmune pathology are the loss of immunological tolerance to self-antigens (which disrupts cellular and cytokine regulation) and the genetic type.

The Role of Cellular and Cytokine Mechanisms in the Disruption of Immunological Tolerance in Autoimmunity Development

Immunological tolerance is essential for maintaining the host's homeostasis and immune system balance. Upon contact with numerous self-antigens — fragments of necrotic or apoptotic cells — the immune system employs specific strategies to prevent autoaggression. Central tolerance (negative selection) is the process of eliminating autoreactive T and B lymphocytes, facilitated

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by 1) the presentation of autoantigens by dendritic cells (DC) as antigen-presenting cells (APCs) and 2) the function of regulatory T cells (Treg). T cells undergo positive and negative selection in their anatomically distinct locations for central tolerance formation in the thymus. Peripheral tolerance is maintained by DC which induce the generation and expansion of Treg cells and regulatory cytokines [1,2].

The functional capacity of DC depends on their subpopulation and stage of maturity. They maintain immunological tolerance by inducing energy and apoptotic deletion of self-antigen-specific T cells and differentiating Tregs. In immune responses, mature conventional dendritic cells (cDCs) are crucial as APC. External pathogen-associated molecular patterns (PAMPs) and internal alarmins or heat shock proteins (HSP) affect conventional DC through membrane Toll-like receptors (TLR) 1–6, TLR8, and intracellular inflammasomes, promoting their maturation. Contact of immature conventional DC, which exhibit low expression of MHC class II antigens and costimulatory molecules, with native T cells supports peripheral immunological tolerance. Therefore, immature conventional dendritic cells can stimulate native T cells to transform into the Treg phenotype and/or support the functions of previously formed Tregs [3, 4].

Adaptive Tregs (aTregs) develop from conventional native T cells in peripheral lymphoid organs. They maintain peripheral tolerance by limiting immunohistopathological changes, suppressing the autoaggressive immune response, and/or maintaining lost tissue homeostasis through transforming growth factor beta (TGF-β) or supporting T and B memory cells through interleukin-10 (IL-10). The $CD4^+CD25^+$ Treg subpopulation expresses Foxp3, a forkhead transcription factor family member implicated in T cell regulation, activation, differentiation, and the development and function of $CD4^+CD25^+$ Tregs. In addition to Foxp3, Tregs express anti-inflammatory molecules IL-10, TGF-β, and IL-35, as well as inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA4), lymphocyte-activation gene 3 (LAG-3), glucocorticoid-induced tumor necrosis factor receptor (GITR), CD39, and CD73. The loss of Tregs function enhances the development of autoimmune processes. In autoimmune diseases, Tregs synthesize regulatory cytokines IL-27 and IL-35, dominant anti-inflammatory cytokines. IL-35 is an inhibitory cytokine required for the maximal suppressive activity of Tregs [1, 4].

Numerous factors influence the development of most autoimmune diseases: 1) the presence of autoantibodies; 2) high levels of type I IFN in the serum of patients; 3) enhanced degradation and destruction of self-cells due to apoptosis, which is characteristic of rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). TLR9 plays a key role in developing autoaggression by ensuring innate immunity's functioning. TLR9 is expressed on dendritic cells and localized in endosomes. Plasmacytoid dendritic cells (pDCs) produce IFN-αβ (type I IFN), which facilitates the recognition and uptake of immune complexes—autoantibodies and "self" autologous nucleic acids—which, after endocytosis, are recognized by TLR9. The DNA ligand CpG-ODN activates pDCs via TLR9, which, in turn, induces the emergence of Tregs. pDCs are key players in establishing oral and transplant tolerance, as they restrain the immune system's reactivity against self-antigens [5]. In conditions of TLR9 deficiency in SLE, the production of antibodies against double-stranded DNA and antichromatin antibodies is inhibited. At the same time, the level of other autoantibodies (particularly anti-Sm) remains stable or even increases. If the immune system does not eliminate apoptotic cells, their fragments trigger the release of inflammatory mediators—nucleosomes, small nuclear ribonucleoproteins, and DNA. Following stimulation by apoptotic bodies and nucleosomes, DCs produce increased levels of TGF-β and decreased levels of IL-6. TGF-β can induce Foxp3 expression and Tregs differentiation even in the absence of DCs. In the periphery, especially in mucosal tissues, $CD4^+$ T lymphocytes transform into peripheral Tregs, which suppress the immune response in an antigen-specific manner. The impairment of peripheral tolerance occurs due to a decrease in the number and functional activity of Tregs—this has been observed in type I diabetes, multiple sclerosis (MS), SLE, and juvenile idiopathic arthritis (JIA). In nonspecific colitis, effector lymphocytes lose their dependence on the suppressive influence of Treg lymphocytes and TGF-β. It has been found that the Treg subpopulation in patients with autoimmune diseases acquires a certain "plasticity," meaning that under the influence of IL-6, they can start synthesizing IL-17. Under the influence of IL-12, they can produce IFN-γ, thus becoming similar to effector cells [1, 4].

Natural autoreactive B cells, specific to autoantigens, highly express TLR9. The level of its expression correlates with high titers of

anti-DNA autoantibodies. TLR9 activates B cells and supports autoimmunity. Autoreactive B cells are found in the bone marrow and peripheral lymphoid tissues, where they are the primary producers of TNF-α in RA synovitis and can also synthesize IL-1, -4, -6, -7, -8, -12, G-CSF, and GM-CSF. The suppressor function of Bregs is mediated by the synthesis of immunomodulatory cytokines IL-10, IL-35, and TGF-β. They facilitate the formation of peripheral Tregs, reduce the synthesis of pro-inflammatory cytokines by dendritic cells, and thereby inhibit the differentiation of the T-helper lymphocyte population. In addition to cytokine-dependent mechanisms, Bregs can suppress autoimmunity in a cytokine-independent manner. Breg cells impede the interaction between T and B lymphocytes in the lymph node. Antigen presentation occurs through the interaction of CD40 and CD80/86 molecules on the B lymphocyte with CD154 (CD40L) and CD28 on the T lymphocyte. Upon binding to the costimulatory protein receptor CD40, B cells begin to synthesize IL-10 and acquire Breg functions. Producing high levels of IL-10 inhibits IL-12 production, leading to a reduced inflammatory response. Bregs regulate the quantity and function of antigen-specific autoreactive T and B cells, DCs, macrophages, and Tregs. The most critical cytokines synthesized by Bregs are B cell activating factor (BAFF) and ligand 13B, a member of the TNF superfamily. Upon contact with a T lymphocyte, BAFF can substitute for CD40L. Thus, the loss of immunological tolerance due to the disruption of its peripheral component, followed by the development of systemic autoimmune rheumatic diseases (SAIRDs), occurs through the dysfunction of DCs, Tregs, and Bregs, as well as alterations in the levels of regulatory cytokines IL-10, IL-35, TGF-β, and BAFF [1, 2, 4].

Genetic Causes of the Loss of Immunological Tolerance to Self-Antigens

Most autoimmune diseases develop on a polygenic basis. Thanks to genome-wide association studies (GWAS), scientists have gained the ability to analyze thousands of single nucleotide polymorphisms (SNP). GWAS research has revealed entirely new risk factors for susceptibility to autoimmune diseases, as many gene products identified through GWAS are associated with immune system functions, inflammation induction, pathogen recognition, complement cascade activation and function, autophagy processes, and lymphocyte differentiation or function regulation. In particular, it has been discovered that polymorphisms in genes encoding CR1, HSP70, FcγRIIA, FcγRIIB, or complement components are implicated in the development of SLE. Patients with RA more frequently exhibit alleles encoding the synthesis of IL-1, IL-1R, or IFN-γ. In contrast, polymorphisms in genes encoding the expression of TLR4 and TLR9 are associated with the development of Crohn's disease. It has also been found that multiple polymorphisms may manifest in a single autoimmune disease [1,6].

Regarding genes encoding major histocompatibility complex (MHC) molecules, the correlation between these genes and the development of autoimmune diseases was the first proof that these diseases are genetically determined. In general, the genetic type of regulation is carried out by MHC molecules encoded by a gene complex on the short arm of chromosome 6. The first and second classes of MHC molecules are collectively called the HLA system (Human Leukocyte Antigens). Proteins encoded by HLA genes serve as markers of "self" for the immune system, allowing it to distinguish between "self" and "non-self." A clear link has been established for genes encoding MHC class II molecules, confirming the critical role of $CD4^+$ T lymphocytes in developing autoimmunity. Studies indicate that MHC class I molecules play a significant role in the pathogenesis of certain autoimmune diseases (Table 1).

Recent advances in medical genetics have identified new disease-risk alleles and loci in patients with systemic autoimmune diseases. In particular, these include genes that determine the signaling pathway of nuclear factor (NF)-κB and T cell-DC interaction. Reports indicate newly discovered single-nucleotide polymorphisms (SNPs) associated with RA development. SNPs of IL-6, signal transducer and activator of transcription (STAT) 4, IL-2RA, CC chemokine ligand (CCL) 21, CD40, CD244, TNF alpha-induced protein (TNFAIP) 3, sprouty-related protein with enabled/vasodilator-stimulated phosphoprotein homology 1 domain (SPRED) 2, recombination signal binding protein for immunoglobulin kappa J region (RBPJ), CC chemokine receptor (CCR) 6, interferon-regulatory factor (IRF) 5, PX domain containing serine/threonine kinase (PXK), cyclin-dependent kinase (CDK) 6, and vitamin D (Vit.D) have been identified in GWAS studies. The heritability of RA has been established at 60%. The inheritance of the ability to produce antibodies against anticitrullinated protein antibody (ACPA) is similar in ACPA-positive

Table 1. **Examples of statistically credible associations between the HLA system and autoimmune diseases [4]**

Disease	HLA Antigens	Risk Percentage, %
Ankylosing spondylitis (Bechterew's disease)	B27	90
Reiter's syndrome	B27	36
Pemphigus	DR4	14
Goodpasture's syndrome	DR2	16
Idiopathic hemochromatosis	A3	9
Chronic active hepatitis	B8	9
Addison's disease	DR3	6
Systemic lupus erythematosus	DR3	6
Myasthenia	DR3, B8	7, 4
Systemic scleroderma	DR2, DR3	4, 10
Rheumatoid arthritis	DR4	4
Type I diabetes	DR4, DR3	5, 4
Graves' disease	DR3	4
Hashimoto's disease	DR11, DR5	3, 3

and ACPA-negative RA patients, at 68% and 66%, respectively. The human leukocyte antigen HLA-DRB1 and alleles with similar epitopes are strongly associated with ACPA-positive RA. The primary genetic susceptibility factor for RA is the presence of specific HLA antigens with genetic variants (37%) [4].

Some autoimmune diseases (RA, SLE, psoriatic arthritis (PsA), systemic sclerosis (SSc), and Sjögren's syndrome (SjS)) are determined by genes that regulate interferon production. The haplotype of Interferon regulatory factor 5 (IRF5), a protein member of the family of interferon regulatory transcription factors, is associated with increased production of type I interferons, which is linked to a higher risk of SLE development. Polymorphism in IRF5 is not only associated with SLE but also with RA, SSc, inflammatory bowel diseases, and multiple sclerosis [5].

MicroRNAs are a novel biomarker used to diagnose disease onset and predict treatment response in patients with systemic autoimmune diseases. These are a class of endogenous, short, non-coding single-stranded RNA molecules (19–23 nucleotides) that function as post-translational regulators of gene expression, particularly genes of pro-inflammatory cytokines. Several microRNAs, such as microRNA-16, -146a, -155, and -223, have been identified in biological samples of patients with systemic autoimmune diseases, and their expression has been confirmed to regulate the course of the disease, activity, and response to medication [7].

Development of the Immune Response to Antibodies in Autoimmunity Formation

A specialized regulatory network operates within the human body to control the immune system's function. The essence of this network lies in the unique ability of antibodies to recognize antigens and to be recognized by other antibodies as antigens, creating a balanced system that regulates the humoral branch of the immune response. It is believed that anti-idiotypic antibodies support antigenic homeostasis in the humoral immune response. An idiotype (idiotypic determinant) is a specific site on antibodies for antigen binding. Idiotypes have a three-dimensional structure and consist of the variable regions of two light and two heavy antibody chains. An idiotype can be an antigen recognized by anti-idiotypic antibodies, which function as a critical part of the regulatory network [1, 4].

B lymphocytes rapidly proliferate upon binding to an antigen, undergoing somatic hypermutation—an essential process for generating high-affinity antibodies specific to a given antigen. Only B lymphocytes that express antibodies with increased affinity survive. Somatic hypermutations predominantly occur in the antibody's hypervariable region; on average, 15 amino acid substitutions per antibody lead to differences between antigenic determinants of a given idiotype. The immune system is intolerant of amino acid chain alterations in idiotypes, which results in the synthesis of anti-idiotypic antibodies. A newly formed idiotype is perceived as "non-self" by

the body and is not recognized as "self" by the immune system. Consequently, peripheral tolerance mechanisms do not eliminate B cells reactive to this antibody. T cells play a crucial role in the regulatory network. Cooperation between T and B cells is antigen-independent, meaning T and B cells can be activated without an antigen. B lymphocytes present peptides of anti-idiotypic antibodies. A low concentration of anti-idiotypic antibodies stimulates T lymphocytes, promoting the synthesis of idiotypic antibodies thereby maintaining equilibrium between B and T cells within the idiotypic network [8].

Antigenic stimulation by autoantigens disrupts this network. The antigen is presented to antigen-specific T cells, which then stimulate B lymphocytes to produce antigen-specific antibodies. This increases the number of idiotypic antibodies, which induce the secretion of anti-idiotypic antibodies. Anti-idiotypic antibodies neutralize autoantibodies and reduce their number while downregulating idiotypic antibody synthesis [8].

It has been demonstrated that in vitro, anti-idiotypic antibodies inhibit antibody synthesis by B lymphocytes. This downregulation of antibody synthesis by anti-idiotypic antibodies affects their binding to both BCR and Fc receptor (FcR) on B lymphocytes. B lymphocytes express only one subtype of FcR—FcγRIIB. This FcR acts as an inhibitory receptor, and through co-ligation with anti-idiotypic antibodies, activated FcγRIIB neutralizes the initiating signal of BCR. Since FcγRIIB is a low-affinity receptor, this inhibitory pathway is only activated by high levels of anti-idiotypic antibodies. If the FcγRIIB threshold is reached, anti-idiotypic antibodies will inhibit antibody secretion, reducing antibody levels. The FcγRIIB-mediated regulatory mechanism that maintains immune response balance is of great importance. FcγRIIB also influences the synthesis and concentration of autoantibodies. Patients with autoimmune diseases, particularly those with active SLE and untreated multiple sclerosis, exhibit reduced levels of FcγRIIB. Elevated levels of autoantibodies particularly characterize these two autoimmune diseases. Furthermore, it has been found that anti-idiotypic antibodies specific to autoantibodies are present in patients in remission and healthy individuals but are absent during disease activation [8, 9].

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibodies against nuclear antigens (nucleosomes, DNA, histones) and phospholipids. The most commonly detected are autoantibodies in SLE target double-stranded DNA (dsDNA). Anti-idiotypic antibodies are not present in most SLE patients; however, they are detected in patients in remission. Thus, in SLE, the levels of anti-idiotypic antibodies inversely correlate with disease activity. In autoimmune thyroid diseases (Graves' disease and Hashimoto's thyroiditis), autoantibodies are directed against three major autoantigens: thyroid-stimulating hormone receptor (TSHR), thyroid peroxidase, and thyroglobulin. Anti-idiotypic antibodies against anti-TSHR antibodies are associated with remission in Graves' disease. In type 1 diabetes (T1D), patients have circulating antibodies against various β-cell antigens — insulin, minor isoforms of glutamate decarboxylase (GAD65), insulinoma 2-associated protein, and zinc transporter 8 protein. These autoantibodies are involved in the pathogenesis of T1D. In T1D patients, anti-idiotypic antibodies against insulin have been detected, suggesting that these antibodies may protect against the development and progression of T1D [10, 11].

Immune-Neuroendocrine Regulation in Autoimmune Diseases

The general interaction between the immune system and the CNS occurs under physiological and pathological conditions. The CNS influences the expression of receptors for various neurotransmitters on immune cells, allowing the brain to modulate immune system functions and maintain homeostasis in the body properly. The endocrine system, particularly the hypothalamic-pituitary-adrenal axis (*HPA*), is one of the systems responsible for regulating the immune system through neural stimuli (e.g., stress). The hypothalamic-pituitary-adrenal axis also influences the hormonal regulation of immune system activity. The main physiological mechanisms controlling the immune-neuroendocrine network (INEN) activity are regulated by hormones, cytokines, neurotransmitters and neuropeptides, which mutually influence each other [12].

The adrenal glands play a significant role in immune response regulation by synthesizing glucocorticosteroids—potent immunosuppressive and anti-inflammatory agents. The glucocorticoid receptor (GR) is present in many immune cells, including dendritic cells, T cells, and neutrophils. Glucocorticoids promote immune cell apoptosis, alter their differentiation levels, suppress cytokine release, inhibit their migration, and

modify interactions between immune cells, weakening the response to exogenous and endogenous antigens. Disrupted activity of the hypothalamic-pituitary-adrenal (HPA) axis is a risk factor not only for severe psychiatric and mental pathological conditions but also for autoimmune rheumatic diseases [13, 14].

Additionally, the HPA axis serves as a fundamental mechanism in the body's response to stress. Reduced activity of the hypothalamic-pituitary-adrenal axis, which can be assessed by measuring the levels of hormones synthesized by the adrenal cortex, may lead to an overactive immune system, potentially triggering the development of many autoimmune diseases. The HPA axis is crucial in inflammation control as cortisol affects innate immunity. Glucocorticosteroids are potentially anti-inflammatory agents that induce apoptosis of monocytes, macrophages, and T cells while suppressing the NF-κB signaling pathway. Such inflammation control is fundamental. However, changing conditions may activate a different mechanism in which the HPA axis enhances inflammation. This phenomenon is known as glucocorticosteroid resistance.

When it develops, the response shifts from a "fight" to a "flight" mode, and inflammation intensifies, especially if it is chronic. Glucocorticosteroid resistance is triggered by chronic stress, which can lead to a reduction in the anti-inflammatory and resolution functions of glucocorticosteroids in prolonged inflammatory processes. High cortisol concentrations may partially explain sensitivity to glucocorticosteroids. This hormone significantly affects acquired (adaptive) immunity, as it can polarize native $CD4^+$ T cells into the Th2 subpopulation, making the patient more susceptible to autoimmune diseases. Stress-induced Th1 response activation enhances IFN-γ production, which protects against neurodegenerative processes. Increased synthesis of Th2-type cytokines and decreased IFN-γ synthesis correlate with memory impairment in the context of moderate chronic stress. Thus, during glucocorticosteroid resistance, cortisol polarizes immune system activity toward a predominant Th2 response [1, 4].

The immune, endocrine, and central nervous systems collaborate during stress through cortisol, norepinephrine, melatonin, and cytokines (particularly IL-1β). IL-1β is produced by glial cells, neurons, and immune cells, and it can penetrate the BBB, causing symptoms of sickness behavior and even aggression, primarily due to its ability to increase norepinephrine (NE). The effect of cortisol is especially significant in glucocorticosteroid resistance, where cortisol increases IL-1β levels instead of reducing them.

High levels of glucocorticosteroids during chronic stress (and depression) act in a reverse manner on the HPA axis, amplifying the signaling pathway of inflammation induction, which, under normal circumstances, should be inhibited. During chronic stress, an increase in IL-1β transforms the inflammatory signal into a neural signal, redirecting it in another direction. Melatonin and cortisol counteract the effects of IL-1β. As a result, a defective interaction reversal occurs, increasing the production of all mediators and disrupting the balance between the immune, endocrine systems, and CNS. An increase in IL-1β levels occurs in all individuals experiencing stressful situations. As a result, the Th1 response is suppressed, and the Th2 response prevails, which can enhance autoantibody production. Various stress factors contribute to the onset or exacerbation of existing SLE, and the autoantibodies characteristic of this disease influence the formation of neuropsychiatric syndromes.

Thus, this article analyzes the consequences of dysregulation in cellular, cytokine, genetic, idiotype:anti-idiotypic, and immune-neuroendocrine types of immune response regulation, which lead to the loss of immunological tolerance and the onset of autoaggression. Moreover, such complex dysregulation creates a foundation on which numerous autoimmune reactions rapidly develop into autoimmune syndromes and progress into autoimmune diseases [15].

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ДИСФУНКЦІЯ РЕГУЛЯЦІЇ ІМУННОЇ ВІДПОВІДІ ЯК БАЗОВА ПРИЧИНА СТАРТУ АВТОІМУНІТЕТУ

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Мета. Дослідити види регуляції імунної відповіді та порушення імунологічної толерантності при автоімунних хворобах.

Методи. Використаний аналіз бібліометричних показників наукових статей та аналітичних матеріалів таких баз даних, як *Scopus*, *Web of Science, DOAJ* і *PubMed*.

Результати. Найважливішими видами регуляції імунної відповіді, які порушуються при автоімунних захворюваннях, є зняття імунологічної толерантності до аутогенів (при цьому клітинний і цитокіновий типи регуляції стають незбалансованими) і генетичний тип. Проаналізовано наслідки дисрегуляції клітинного, цитокінового, генетичного, ідіотип-антиідіотипового та імунонейроендокринного типів, які викликають порушення імунологічної толерантності та початок аутоагресії.

Висновки. Наслідки дисрегуляції імунної відповіді, яка спричиняє відміну імунологічної толерантності створює грунт, на якому численні автоімунні реакції швидко сформовуються в автоімунний синдром і переходять в автоімунні хвороби.

Ключові слова: імунна відповідь, імунологічна толерантність, Tregs, автореактивні В-клітини, апоптичні клітини.