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IMMUNOPATHOGENESIS OF MYASTHENIA GRAVIS (REVIEW)

Abstract

Myasthenia gravis is a progressive autoimmune disease, which is characterized by the production of antibodies against the structures of the neuromuscular junction. High clinical heterogeneity of autoimmune myasthenia and the initiating course of the disease increase the urgency of its pathogenesis studying, searching for specific methods of marker diagnostics, developing algorithms for predicting the features of the development of the disease. At the present time, there are different approaches to the study of the etiology and pathogenesis of the disease, which include serological, biochemical, genetic, etc., theories of its development. For decades, researches have been carried out to find new pathogenetic links in myasthenia gravis. Today, a number of antibodies were described, such as antibodies against muscle-specific tyrosine kinase (MuSK), ryanodine receptors, titin, lipoprotein bound receptor 4, cortactin, etc. The serological diagnosis of myasthenia gravis has been used as a "gold standard" in clinical practice. The prognostic criteria describing the course of myasthenia gravis and the type of antibodies isolated in the blood serum of the patient are described. Mechanisms of immunological tolerance disorder, which triggers the production of antibodies against their own structures, have already been developed as well, and their genetic bases are also described. Thanks to the development of biotechnological methods, the researchers were able to identify the subtype of lymphocytes involved in the development of myasthenia gravis. Isolation of individual subpopulations of lymphocytes also became available. Researchers continue to search for new targets, allowing to improve diagnostics, to develop new directions in the therapy of the disease. However, despite the active study of various mechanisms for the development of myasthenia gravis, many unresolved problems still remain. The article briefly describes the main investigated mechanisms of complex myasthenia gravis pathogenesis.

Key words: *autoimmune myasthenia gravis, myasthenia gravis pathogenesis, myasthenia gravis markers*

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HLA — major histocompatibility complex system, LRP-4 — low-density lipoprotein receptor-related protein 4, MuSK — muscle-specific tyrosine kinase, T_{reg} — regulatory T cells, TCR –T cell receptor, ILs — interleukins, Th — T-helper cells, TNF — tumor necrosis factor

Myasthenia gravis is an autoimmune disease, which is based on mechanisms aimed at the synthesis of antibodies against the neuromuscular junction structures. The causes triggering the breakdown of immunological self-tolerance are not completely defined. It is considered to be a multifactorial disease [9, 10].

The disease has a high clinical heterogeneity, a chronic progressive course, affects mostly young people, and it is debilitating in nature [3, 51, 68, 70, 96]. Autoimmune myasthenia gravis is the most common neuromuscular pathology, accounting for up to 60% of patients [2]. Despite the widespread prevalence [16], the pathogenesis of myasthenia gravis remains poorly understood due to the diversity of antigenic "targets" of the neuromuscular synapse [9].

Active research into autoimmune diseases, including myasthenia gravis, has been going on for decades. The attention of scientists is attracted both by serological and immunological, and genetic features, endogenous and exogenous factors [8]. In addition, myasthenia

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pathogenesis may also involve proteins (for example, survivin), cellular (micro-RNA) structures, synaptic cholinergic receptors, changes in the structure of the ion channels of axon, muscle structures, etc. [10, 44].
Recently, the role of survivin protein in the pathogenesis of autoimmune myasthenia gravis has been studied. It is functionally important for cell division, apoptosis and, possibly, for the biogenesis of micro-RNA. It also takes part in the implementation of adaptive immune reactions, controls the differentiation of memory CD4+ and CD8+ T cells and maturation of B cells. In the literature, there is evidence supporting the possible application of survivin as a diagnostic and prognostic marker for rheumatoid arthritis, psoriasis, pulmonary arterial hypertension, multiple sclerosis, inflammatory bowel disease, and myasthenia gravis [36, 56].
According to a number of scientists, components of the complement system participate in the blocking of neuromuscular transmission, which is clinically manifested by the development of muscular fatigue. Blocking the activity of the complement system in patients brought about relief of the disease symptoms [24, 25, 43, 99].
In the history of the study of the pathogenesis of autoimmune myasthenia gravis, definite success has already been achieved. A number of antibodies against antigenic structures in myasthenia have been identified, which can serve as an additional diagnostic criterion for this disease and provide a source of information that allows for the course of the disease to be predicted [1, 65, 69].
Analysis of the concentration of serum markers is the standard for diagnosis of the disease. In the genetics of the disease, a number of HLA-system genes have been identified whose polymorphisms have an impact on the development of myasthenia gravis.

The authors of the article tried to describe the existing directions in the research of pathogenesis of autoimmune myasthenia.

The Role of Antibodies in the Pathogenesis of Myasthenia Gravis

The method for determining marker antibodies is widely used in the diagnosis of autoimmune diseases [34, 121]. A number of serological markers related to myasthenia gravis have been described in the literature [107]. These data emphasize the diversity of mechanisms of pathogenesis and, perhaps, explain the existence of differences in clinical manifestations [44, 66].
Determination of the antibody titer to the structures of acetylcholine receptors is one of the criteria for the diagnosis of seropositive myasthenia gravis. According to the literature, exceeded reference values are recorded in 80–85% of patients, among whom patients with the generalized form predominate [1, 106].
Epidemiological analysis of patients revealed a bimodal distribution of increased titer of antibodies against acetylcholine receptors. Seropositive patients prevailed among women between the ages of 20 and 40, and men of the elderly age group of 60–80 [44].
In addition to subunits of the nicotinic receptor, a number of other postsynaptic structures (muscle-specific tyrosine kinase, lipoprotein-bound receptor protein 4 — LRP4), and of muscle tissues (titin, ryanodine receptors, agrin) have immunogenic properties [48, 106].
Approximately in 70% of cases of seronegative myasthenia gravis antibodies against muscle-specific tyrosine kinase (MuSK) are detected. Moreover, in many of these cases, there is a tendency for the disease to take a severe course, when the respiratory and bulbar muscles are predominantly affected. Such forms of the disease rarely respond to hormonal therapy and require the prescribing of combined immunosuppressive therapy [1, 27, 72, 73, 82, 121].
Antibodies against LRP4 are detected in 2–27% of cases in double-seronegative patients (antibodies against acetylcholine receptor and MuSK in the blood are not detected). Among LRP4-positive patients, female patients predominate (2:1), muscle weakness is moderate. The distribution in muscle groups is similar to seropositive patients, but in the fifth part is limited only to ocular manifestations. They have shown a positive response to inhibitors of acetylcholinesterase [1, 91, 106, 118].
Another component of the postsynaptic membrane is agrin. Neuronal agrin is a protein of the extracellular matrix used by motoneurons to induce clustering and post-functional differentiation of acetylcholine receptors. Agrin binds to LRP4 to form a tetrameric complex that interacts with MuSK and activates it to initiate subsequent signaling pathways [30].
According to F. Romi and other researchers, the study of antibodies against striated muscle tissue in the serum of seronegative patients should produce promising results. These include antibodies against the components of striated skeletal or cardiac muscle (SH antibodies), antibodies against citric acid extract

of striated muscle (CAE antibodies) and antibodies against titin and ryanodine receptor (RyR), which are used in the diagnosis of myasthenia gravis associated with the presence of thymoma. Among them, the determination of a combination of serological indicators for muscle tissue, especially for titin and ryanodine receptor, is the most sensitive and specific to detecting thymoma [47, 97].

Antibodies that attack potassium channel structures were recorded in 12–28% of patients with myasthenia gravis in Japan. The presence of these antibodies is associated with bulbar disorders, possible myasthenic crises, thymoma, myocarditis and prolonged QT intervals on electrocardiograms, and the detection of neuromyotonia in an electrophysiological study. However, in the European population, these markers are isolated in patients with local forms of myasthenia gravis, mainly the ocular form, in which the signs of neuromyotonia are not detected by EMG [86].

In some patients who were classified as double-seronegative, antibodies against cortactin, a key regulator of actin reorganizations in response to changes in tyrosine kinase signaling, were detected by Gallardo E. in 2014 [57]. It is known that actin chains play an important role in various cellular processes aimed at remodeling of the plasma membrane and the movement of intracellular vesicles and particles. Cortactin is exposed to tyrosine kinases. Its phosphorylation reduces the activity of Src family kinases. Phosphorylation of cortactin provides binding sites for specific signaling proteins in SH2 domains, which can regulate a number of cellular functions. It should also be noted that cortactin is expressed in breast cancer and squamous cell carcinoma of the head and neck [12, 28, 53, 57, 87].

Analysis of serum antibodies against the structural components of neuromuscular junction is an important tool that is used in healthcare practice. A variety of serological markers can be used to predict the character of the clinical course.

The Role of Cytokines in the Pathogenesis of Myasthenia Gravis

Cytokines play an important role in the development of autoimmune diseases, determining the intensity of inflammatory changes in tissues, including neuromuscular structures [101, 103, 115].

As mediators, they take part in the differentiation of immunocompetent and hematopoietic cells and in the formation of mechanisms responsible for the intercellular interaction underlying the immune response. Their main biological activity is the regulation of the immune response at all stages of its development [117]. In general, it should be noted that all this large group of endogenous regulators participates in the division and differentiation of progenitor cells of functionally active immunocompetent cells, in the changing of antigens and various markers expression, in the chemotaxis, in the switching of immunoglobulin synthesis, in the inducing cytotoxicity in macrophages, in the proliferation of antigen-sensitive lymphocytes, in the differentiation of B cells to the producers of immunoglobulins, in the switching of the immunoglobulins synthesis from one isotype to another, in the ensuring the maturation of progenitors of cytotoxic T cells to the mature effectors, in the inducing cytotoxicity in macrophages, and in the formation of the inflammation site [101, 103].

Cytokines play a coordinating role in the pathogenesis of autoimmune diseases. They participate in the interactions between B lymphocytes and T helpers (Th) [15]. So, the cytokine can affect the receptors of the very cell that synthesizes it, and it can also affect the adjacent cells as well as the cells of distant organs. Yilmaz et al., 2015, have shown on the experimental model of autoimmune myasthenia gravis that a decrease in the number of cytokines correlates with a decrease in the level of antibodies against acetylcholine receptors. Scientists have identified a relationship between an increase in the level of TNF-α (tumor necrosis factor α), interleukins 17A and 21 (IL-17A and IL-21) and the severity of the disease with MuSK-positive myasthenia gravis [15, 117].

TNF inhibits the activity of regulatory T cells, which reduce the autoreactivity of immunocompetent cells, while reducing TNF levels results in the restoration of the function of these cells [55].

The ability of IL-10, which is synthesized by regulatory type 1 T cells, to inhibit the activation of effector immune cells during autoimmune responses, underscores their essential role in maintaining immune tolerance. Interleukin-27 (IL-27), a member of the IL-12 family of heterodimeric cytokines, has been identified as an important cytokine that suppresses the Th17 cell effector and promotes the formation of Th1 cells [81].

Th17 cells are involved in the development of autoimmunity. T cells producing IL-17 and IL-10 are functioning in the suppression of inflammatory reactions [3, 38, 59, 69, 72, 77, 83, 88, 108]. IL-17 is

present in sites of tissue inflammation in autoimmune diseases [40]. T helper cells also synthesize IL-23, which contribute mechanisms that upset self-tolerance in the central nervous system [58].
Scientists have used the experimental model of myasthenia to show that IL-12 is the determinative cytokine for the differentiation of Th1 cells that are involved in the development of myasthenia gravis, and IL-10, which is a powerful differentiation factor for B cells, also promotes the development of myasthenia gravis. In contrast, IL-4 has an antagonistic effect. It inhibits the development of symptoms of myasthenia gravis. An increase in the level of IL-10 in the patients with generalized myasthenia gravis is significantly higher than in patients with a local form of the disease [67, 74, 116].

A number of scientists have shown that in patients receiving immunosuppressive therapy, the number of memory cells increases. When stimulating CD40 in patients with myasthenia, significantly lower levels of IL-10 and IL-6 were obtained than in the control group. When stimulating CD40 and B cell receptor in addition to these cytokines, the production of TNF-α also decreased [116, 117].
The works of Akiyuki Uzawa et al. (2016) have demonstrated that in the blood serum of seropositive patients there is an increase in the content of IL-15, IL-19, IL-20, IL-28A, IL-35, which induce ligand proliferation, which is a vascular endothelial growth factor. Changes in the cytokine profile in patients indicate the role of these molecules in the development of myasthenia gravis [101, 102].
Perhaps, the detection of changes in the cytokine profile in myasthenia patients can function as an important prognostic factor in diagnosis, and it can also be used in the development of medicines with a new mechanism of action.

The Role of Immune Cells in the Pathogenesis of Myasthenia Gravis

The protective function of the immune system is provided by its ability to recognize practically the full range of pathogens, the presence of immunological memory, which is designed to produce a rapid response, and immunological tolerance, which makes it possible to avoid damaging own body structures [33, 62]. It is known that the main reason why a large amount of autoantibodies are released in the organism is the positive selection of autoreactive T cells and the selective loss of regulatory T cells. In connection with this, another direction in the research of the characteristics of pathogenesis of myasthenia gravis is represented by the study of self-tolerance mechanisms at the intercellular level [33].
By participating in the formation of immunological memory, in recognizing antigens and inducing immune response, T cells are one of the key links in the pathogenesis of autoimmune diseases. T-lymphocytes also have the ability to recognize antigens on the surface of antigen-presenting cells in combination with their own histocompatibility antigens [7, 26, 32, 62, 74].
There are several types of T cells. Populations of T cells differ both in membrane markers and in the method by which antigens are recognized and functions are performed. A receptor complex with a unique structure, which determines the functioning of T cells, functions on the surface of T cells. In addition to the main receptor complex, a number of auxiliary protein complexes, co-receptors, have a pronounced presence on the surface. CD4 and CD8, CD3, CD28 are the most significant auxiliary receptor complexes. The functionally important co-receptors CD4 and CD8 are associated with tyrosine kinase systems and a costimulatory molecule [99].
Part of the T cells is involved as cytotoxic cells, significantly reducing intense immune response and autoaggression and acting as regulatory T cells (T_{reg}). In barrier tissues, they interact with epithelial cells, stimulating their survival and functions and facilitating the recovery of the epithelium when it is damaged [71, 108, 113].
Natural regulatory T cells prevent other T-lymphocytes from reacting to their own antigens, limiting all forms of immune response. It is these cells that guarantee the suppression of the activity of autoreactive cells, which have avoided negative selection during development. In addition, when regulatory cells are differentiated, other functionally important membrane molecules have a pronounced presence on their surface [71, 112].
Scientists also found a decrease in the suppressive activity of lymphocytes when there is a defect in the structure of T_{reg} [33, 108].
T_{reg} cells are a subpopulation of T cells that inhibit the activation of other immune cells and thereby support

the homeostasis of the immune system. The influence of T_{reg} cells on the pathogenesis of autoimmune diseases, including myasthenia gravis, is actively being studied by a number of researchers from different countries. The researchers suggest that the functional deficiency of T_{reg} cells can lead to the inability to suppress autoreactive T cells [65, 67, 109, 114].

The effect that is produced on these cells, according to some researchers, presents a promising direction in the therapy of autoimmune disorders. According to a number of researchers, regulatory T-lymphocytes represent the most promising area in the study of the pathogenesis of myasthenia [97, 107].

In addition to T cells, B cells also participate in the development of myasthenia gravis by producing autoantibodies. The study of cellular mechanisms that participate in the development of autoimmune disease is a promising direction for targeted therapy [10, 21, 23].

The study of the disrupted functioning of regulatory T cells, which are associated with the severity of the disease, has attracted a great deal of interest from scientists. Approaches are actively being developed to improve and even to correct the functioning of T-lymphocytes, which can be used in the treatment of myasthenia gravis and other diseases [31, 33, 92, 98, 99].

The Role of Receptors and Enzymes in the Pathogenesis of Myasthenia Gravis

The result of all interactions occurring at the cellular level is chemical transformations. Earlier, the study of the cascade of signaling pathways was impossible due to technical reasons, and scientists could only guess about the possible role that certain biological substances played. External factors affecting the receptors of the cell membrane lead to conformational changes in their structure, thereby leading to the activation of enzymatic systems that play a role of secondary intermediaries in signal realization [94, 104].

Another direction in the research of myasthenia gravis pathogenesis and other autoimmune diseases is the study of a cascade of signaling pathways that ensure the functioning of immune cells. At different stages of signal transmission, this functioning is carried out by enzyme molecules (mainly protein kinases that activate proteins at each next stage of signal transmission) as well as adaptor and GTP-binding proteins [6, 113].

The most promising in the study of the pathogenesis of myasthenia are T-cell receptor associated signaling pathways, which are determined by the interaction of the main lymphocyte receptor with coenzyme molecules as well as Toll-like receptor signaling pathways [4, 11, 17, 22, 45, 52, 77].

The end product is the transcription factors that lead to a change in gene activity resulting from the enhancement or suppression of the secretory function of cells in the immune system [93].

T cell receptor (TCR) determines the functional activity of each T-lymphocyte, which is the most important structure on the lymphocyte membrane. The receptor makes it possible to recognize only antigen fragments associated with histocompatibility molecules. Each T cell has its own unique receptor. Each TCR is strongly associated with CD3 as well as with CD4 or CD8 co-receptor molecules [38]. TCR and co-receptors are bound by an enzyme of non-receptor Src family tyrosine kinases (Fyn, Blk, Lyn in B-lymphocytes, Lck and Fyn in T-lymphocytes) [112].

Its dephosphorylation occurs when there is antigenic stimulation with the participation of phosphatase CD45, which causes it to be activated. Activated Src kinase (Lck) phosphorylates ITAMs* that are bound to the receptor, which increases the activity of another kinase, Zap70, which begins to phosphorylate the adaptor proteins: LAT (Linker for Activation of T cells) and SLP-76, BLNK and SLP-65 [109, 114]. Adaptive proteins, binding to enzymes (tyrosine kinases) of the Tec family, increase the activity of one of the most important key enzymes — the phospholipase Cγ, which breaks up the phosphatidylinositol biphosphate on the cell membrane for phosphatidylinositol triphosphate and diacylglycerol. These molecules trigger activation of the pathways responsible for the function of transcription factors NF-kB, NFAT and AP-1, initiating the transcription of genes responsible for the differentiation, proliferation, and effector activity of T cells [89].

In the generation of signals transmitted from the polypeptide chains of the TCR-CD3 complex, the presence in the cytoplasmic part of the complex of the ITAM activation sequence associated with ZAP-70 is the key factor in the signal transmission from TCR when it binds to the ligand [76, 109, 111, 114].

* ITAM — (Immunereceptor tyrosine-based activation motif) — tyrosine-containing activation sequences of amino acids in immunoreceptors.

In addition to CD45, another key regulator of the activation cascade of transcription factors affecting the functioning of immunocompetent cells is presented by PTPN22, an immune homeostasis regulator that inhibits T cell receptor signaling and the selective promotion of type I interferons, which affects ZAP-70 activity by Lck kinase after activation of receptors [29, 49].
It should also be noted that the T cell receptor, due to the fact that it binds to other molecules and co-receptors, can transmit both strong and weak signals, which are necessary both to maintain cell survival at the periphery and to create self-tolerance mechanisms [112].
Pathologies in the structure of this complex can thus cause the malfunctioning of T cells and the development of autoimmune diseases such as autoimmune diabetes, systemic lupus erythematosus, and systemic scleroderma [46]. Since most autoimmune diseases are considered antigen specific, the pathology in the T cell receptor structure, or the disruption of its functional activity, play a decisive role in the pathogenesis of diseases [13, 89].
Each receptor complex has connections with the intracellular system of enzymes, and the most important are tyrosine kinases and phosphatases.
The function of tyrosine kinases lies in the substrate phosphorylation of tyrosine groups of the target proteins. These are responsible for their activation and the manifestation of cell functions. The role of PTPN22 and CD45 in the development of several autoimmune diseases has been demonstrated the most conclusively, and there are some reports on their role in the pathogenesis of myasthenia gravis [14, 31, 61, 77, 105].
The main role in the transfer of receptor kinases to the "working" state is performed by the molecule CD45, in which tyrosine phosphatase (double) is active. CD45 deficiency leads to the development of manifestations of severe combined immunodeficiency. CD45 serves as a genetic modifier for autoimmune, infectious, and malignant diseases. Its prominence is limited to all nuclei of hematopoietic cells. In general, it becomes more prominent as the cells mature. There are several isoforms whose functional activity affects the functioning of T cells [105].
Some studies have shown a reduction in the prominence of CD45 in patients with SLE in comparison with the control group. However, information on the possible involvement of CD45 in the pathogenesis of myasthenia gravis is contradictory [54, 84].

Another enzyme that plays the role of a potent inhibitor of activation of T cell signaling is PTPN22, due to dephosphorylation processes. It suppresses the function of Lck and Fyn and activates the Lyp-enzymatic pathway [20, 29, 37, 80, 82].
A number of studies have shown the association of PTPN22 with the development of diseases such as type 1 diabetes, rheumatoid arthritis and SLE, as well as its role in increasing the risk of developing juvenile idiopathic arthritis, thyrotoxicosis, autoimmune thyroiditis, myasthenia gravis, generalized vitiligo, and others belonging to the group of autoimmune diseases [14, 61].

The Role of Genes in the Pathogenesis of Myasthenia Gravis

According to modern data, the mechanisms that disturb tolerance to autoantigens are associated with changes in expression of autoantigens caused by exposure to harmful factors as well as genetic peculiarities. Many genetic factors affect the predisposition and onset of the disease [19, 35]. It is known that the lack of immune response to its own antigens is a consequence of the formation of immunological tolerance at a certain stage of individual development. There are both active and passive mechanisms for the formation of self-tolerance. The passive mechanism is the ignoring of autoantigens by the immune system, which is caused by their low concentration or by the isolation from it. The active ones include elimination of autospecific clones, correction of autoreceptor genes, induction of anergy of autospecific clones, and inhibition of immune response by regulatory cells. Currently, the search for new candidate genes involved in the pathogenesis of the disease is underway [18, 19, 60].
More than thirty years ago, the genes of the HLA-system (major histocompatibility complex (MHC) class II locus)* were identified, which are associated with an increased risk of myasthenia gravis [39, 50]. During studies that were conducted over the last decade, such genes as the gene of the type 22 protein

* MHC (abbr. of English *Major Hystocompatibility Complex*) in humans was later described in the works of J. Dosse. It has been designated as HLA (abbr. of English *Human Leukocyte Antigen*) in humans, as it is associated with leukocytes. There are two main classes of MHC molecules: it is conditionally accepted that MHC class I induces a predominantly cellular immune response while MHC class II produces a humoral response.

tyrosine phosphatase non-receptor (*PTPN22*), *TNFAIP3* — the gene of interacting proteins 1 (TNIP1), the gene of cytotoxic T-lymphocyte protein 4 (*CTLA4*), , and a number of other genes have been identified [19, 24, 64].

An association with these genes has also been revealed in pediatric patients [42]. This fact can become an argument in favor of the theory of unified genetic mechanisms for the formation of neuromuscular transmission disorders.

It is believed that the relationship of myasthenia with a number of other autoimmune diseases has recently become more evident, many patients often have a serious medical history or family medical history with a number of other diseases, the associations of myasthenia with autoimmune thyroiditis, rheumatoid arthritis, and type 1 diabetes are mentioned most often [31, 75].

According to different authors, in the youngest patients the most frequent myasthenia gravis is associated with the genes *PTPN22* (a gene that encodes tyrosine phosphatase*, where defects lead to an increase in autoreactivity), *HLA* and *TNFAIP3* [63]. The key genes involved in the development of myasthenia gravis are *IRF5* (the gene of the interferon-5 regulatory factor), *TNFAIP3* (the gene of predisposition for TNF-α-induced protein 3, also known as A20), and the interleukin-10 gene (*IL10*); the genes *TNFSRF11* and *CTLA4*** are associated with myasthenia gravis in the elderly because of their regulatory function.

Therefore, it is advisable to study the role in the development of myasthenia of those genes, which are related not only to the HLA system [19, 39].

Conclusion

There are currently still many questions regarding the characteristics of pathogenesis of myasthenia gravis. Researchers continue to search for new targets that make it possible to improve diagnosis and to develop new directions in the treatment of disease. In addition to the antibodies that target acetylcholine receptors that were isolated in the 70s and 80s, other antibodies (that target MuSK and ryanodine receptors, titin, lipoprotein-bound receptor 4, etc.) have also been identified. Differences in the clinical manifestations of myasthenia in patients with different serological markers have been described.

With the development of biotechnological methods, researchers were able to identify the subtype of lymphocytes involved in the development of myasthenia gravis. It became possible to separate individual populations of lymphocytes from the patient's blood and to study their function *in vitro*. The development of genetic technologies and decoding of the human genome has made it possible to investigate the role of genes that are related to more than just the HLA system in the pathogenesis of myasthenia gravis. However, despite the active research of various mechanisms by which myasthenia gravis develops, many unresolved problems still remain.

The successes that have been achieved are prerequisites for the search for new therapeutic targets. Every year, the number of studies that seek to compare clinical manifestations depending on the serological and genetic characteristics of patients continues to grow [41, 68, 111].

Conflict of Interests

The authors declare no conflict of interests.

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* Tyrosine phosphatase functions as a key regulator of immune homeostasis. Normally, it inhibits the transmission of T cell receptor signals and selectively stimulates the response of type I interferon in myeloid cells. When it has a defect, it results in an increase in autoreactivity [14, 61, 95].

** Synthesis of the CTLA4 gene is higher in the activated T cells. It increases T cell mobility and reduces contact periods between T cells and antigen-presenting cells, which leads to a decrease in cytokine production and proliferation. The defect of the CTLA4 gene has a significant effect on the T cell component of immune system regardless of age [98].

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