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# IMMUNE RESPONSE AGAINST EPSTEIN-BARR VIRUS AS AN ETIOLOGIC FACTOR AND THERAPEUTIC TARGET FOR MULTIPLE SCLEROSIS

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**Introduction.** The etiology of multiple sclerosis (MS) remains unknown. According to the current consensus, susceptibility to MS is due to an elaborate interaction between genetic predisposition and multifactorial environmental factors, including vitamin D deficiency, smoking, inflammatory diet, psychoemotional stress, and infections. With regard to the infectious component, for decades, MS has been associated with a prior infection with the Epstein-Barr virus (EBV). However, it remains unclear why only a limited proportion of the numerous EBV-infected population develop MS.

**Objective.** To discuss the factors of interaction between the immune system and EBV that predispose to the development of MS, as well as to analyze the possibilities of their use as therapeutic targets for the prevention and treatment of MS.

**Discussion.** The results of a recent large epidemiologic study have provided new evidence for the association between EBV and MS. It has also been shown that cross-reacting antibodies to myelin sheath antigens can be detected in the blood of patients with EBV. However, most patients with EBV do not develop MS. This is probably due to the elimination of autoreactive cells. Natural killer (NK) cells play a particularly important role in this process. In MS, NK-mediated elimination of autoreactive B cells may be impaired. In this regard, an add-on therapy of MS aimed at controlling EBV-induced autoimmune responses appears promising.

**Conclusions.** Reduced cytotoxic activity of NK cells against cells that show cross-reactivity to EBV antigens and components of the myelin sheath is among the factors of interaction of the immune system with EBV that contribute to MS development. As an add-on therapy for MS, it may be reasonable to use agents that reduce the presence of EBV in the organism and have a favorable safety profile (e.g., curcumin and quercetin). The search for agents that can improve immunological control of autoreactive cells is also promising. Such agents may include compounds that are capable of enhancing the activity of NK cells, for instance, urolithin A, curcumin, and alloferon.

**Keywords:** multiple sclerosis; Epstein-Barr virus; autoreactive cells; natural killer cells; NK cells; polyphenols; curcumin

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# ИММУННЫЙ ОТВЕТ НА ВИРУС ЭПШТЕЙНА-БАРР КАК ЭТИОЛОГИЧЕСКИЙ ФАКТОР И ТЕРАПЕВТИЧЕСКАЯ МИШЕНЬ ПРИ РАССЕЯННОМ СКЛЕРОЗЕ

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**Введение.** Этиология рассеянного склероза (РС) остается неизвестной. Современное консенсусное мнение заключается в том, что восприимчивость к РС обусловлена комплексным взаимодействием между генетической предрасположенностью и многофакторным влиянием внешней среды, включая такие факторы, как недостаток витамина D, курение, приверженность воспалительной диете, инфекции, психоэмоциональный стресс. Что касается инфекционного компонента, на протяжении десятилетий РС ассоциировался с предшествующей инфекцией, вызываемой вирусом Эпштейна-Барр (ВЭБ). Однако вопрос о том, почему лишь небольшая доля популяции, инфицированной ВЭБ, заболевает РС, остается открытым.

**Цель.** Определение факторов взаимодействия иммунитета с ВЭБ, предрасполагающих к развитию РС, а также анализ возможностей их использования в качестве терапевтической мишени для профилактики и терапии данного заболевания.

**Обсуждение.** Результаты недавнего крупного эпидемиологического исследования привнесли новые доводы в пользу связи ВЭБ и РС. Было показано, что в крови носителей ВЭБ можно обнаружить антитела, перекрестно-специфичные к антигенам миелиновой оболочки. Несмотря на это, у большинства носителей ВЭБ РС не развивается. Вероятной причиной является своевременное удаление аутореактивных клеток. Особо важную роль в этом процессе играют NK-клетки. При РС нарушаются процессы NK-опосредованной элиминации аутореактивных В-клеток. В этой связи перспективна дополнительная терапия РС, направленная на контроль аутоиммунных реакций, вызванных ВЭБ.

**Выводы.** Среди факторов взаимодействия иммунной системы с ВЭБ, способствующих развитию РС, следует отметить сниженную цитотоксическую активность NK-клеток против клеток, проявляющих перекрестную реактивность к антигенам ВЭБ и компонентам миелиновой оболочки. В качестве дополнительной терапии РС может быть обоснованным применение средств, способных снижать представленность ВЭБ в организме и обладающих благоприятным профилем безопасности, в частности куркумина и кверцетина. Также перспективен поиск средств, способных усиливать иммунологический контроль над аутореактивными клетками. К таким средствам могут относиться соединения, способные усиливать активность NK-клеток, в частности уролитин А, куркумин, аллоферон.

**Ключевые слова:** рассеянный склероз; вирус Эпштейна-Барр; аутореактивные клетки; естественные киллеры; NK-клетки; полифенолы; куркумин

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## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune inflammatory demyelinating disease of the central nervous system (CNS) of unknown etiology. The development of MS is associated with an elaborate interaction between a genetic predisposition and multifactorial environmental factors, including psychoemotional stress, vitamin D deficiency, smoking, changes in the microbiota, and infections [1–3]. Among the infectious component of the etiology and pathogenesis of MS, the association of MS with the Epstein-Barr virus (EBV) can be singled out. About 100% of MS patients are seropositive for EBV [4]. However, while this relationship has been known for a long time, only a small proportion among 90% of the adult population chronically infected with the EBV virus develop MS [1, 2].

Despite its usually subclinical activity, EBV is associated with various tumor and autoimmune diseases. EBV exhibits a fairly profound effect on the immune system, being the most common causative agent of infectious mononucleosis, as well as some fatal lymphoproliferative diseases in immunosuppressive conditions. An increasing amount of data is emerging on EBV infection as a major risk factor in the development of a number of autoimmune diseases, in particular MS [5, 6]. Therefore, it appears relevant to elucidate those features of the immune response against EBV that trigger the subsequent development of MS.

In this work, we set out to determine factors in the interaction of immunity with EBV that predispose to MS development, as well as to analyze the possibilities of their use as a therapeutic target in the prevention and treatment of this disease.

## MATERIALS AND METHODS

The search for, systematic analysis, and review of scientific literature was carried out in electronic bibliographic databases in the Russian (eLibrary) and English (PubMed) languages. The search queries included the following keywords: multiple sclerosis, Epstein-Barr virus, autoreactive cells, natural killer cells, NK cells, polyphenols, curcumin. The search depth was 10 years. The inclusion criterion was the availability of data on the results of cohort studies, randomized controlled trials, and preclinical studies.

## RESULTS AND DISCUSSION

### Epstein-Barr virus in the etiology and pathogenesis of multiple sclerosis

The presence of a close relationship between EBV and MS has been discussed for a number of years, based on data on an increased risk of MS developing after infectious mononucleosis (in the form of symptomatic primary EBV infection) and in patients with high titers of antibodies to specific EBV antigens [7]. The results of a recent extensive epidemiological study by Bjornevik et al. [8] have provided new arguments in favor of the connection between EBV and MS. The hypothesis that MS is caused by EBV was tested in a cohort of more than 10 million young people. According to the results of the study, the risk of MS increased 32-fold after infection with EBV. However, infection with other viruses did not lead to an increased risk of MS, including cytomegalovirus (CMV), which is transmitted in a similar way. The levels of serum light chains of neurofilaments (an indicator of axonal degeneration, one of the diagnostic MS markers) increased only after the production of antibodies to EBV antigens. The authors argue that these results cannot be explained by any known risk factor for MS and may imply that EBV is the leading cause of MS.

The consequences of EBV infection vary, depending on age and genetic factors. The risk of developing infectious mononucleosis and MS is likely to grow when primary EBV infection occurs after the age of 10. At this age, the negative selection of autoreactive T cells slows down and the cell-mediated response of Th-1 cells reaches its peak. Most people are diagnosed with MS between the ages of 20 and 50, several years after becoming infected with EBV. The EBV persistence increases the survival of memory B cells and causes long-term changes in the cytokine response of the host [5, 6].

Nevertheless, the question concerning why only a small proportion of numerous EBV carriers develop MS remains to be elucidated. Moreover, it remains unclear how EBV is involved in the etiology and/or pathogenesis of MS. When answering the second question, literature data offers two main hypotheses [9]. Firstly, persistent infection and reactivation of the virus can serve as a stimulus for chronic inflammation inside and outside the nervous system, either directly or by creating a long-term pool of pro-inflammatory B lymphocytes. Secondly, autoimmune reactions can be caused by molecular mimicry of antigens common to EBV proteins and CNS antigens, which was shown, in particular,

for the glial cell adhesion molecule (GlialCAM), the main protein of myelin, and others [9]. It has been mentioned above that the relationship between MS and EBV has been established for quite a long time; however, more evidence has recently emerged to support the second of the above hypotheses.

### Role of NK cells in providing immune tolerance in the presence of autoimmunity to CNS antigens

The regulatory role of natural killer (NK) cells was described more than 20 years ago [10]. In recent years, new evidence of the possible role of NK cells in immunological tolerance and their protective value against various autoimmune diseases, including MS, has emerged. In the context of immune regulatory properties, special attention is paid to $CD56^{bright}$ NK cells, which play an important role in controlling the T cell response and maintaining homeostasis. This subpopulation of NK cells owes its name to the high surface expression of CD56 (nerve cell adhesion molecule), being also characterized by the expression of $CD16^{dim}$ and the NKG2A inhibitory receptor and, at the same time, the absence of expression of immunoglobulin-like receptors of killer cell immunoglobulin-like receptors (KIR). $CD56^{bright}$ NK cells possess reduced cytotoxicity compared to $CD56^{dim}$ NK cells, which renders them regulatory. It was shown that therapy with various multiple sclerosis disease-modifying medications (MSDMM) increases the relative number of NK cells, as well as NK-mediated immune regulatory functions [11].

$CD56^{bright}$ NK cells express receptors for various cytokines, such as interleukin (IL)-12, IL-15, and IL-18, which are produced by activated antigen-presenting cells. The response to these cytokines can cause proliferation of $CD56^{bright}$ NK cells and their production of a number of cytokines, including IFN-γ, IL-13, and GM-CSF (granulocyte-macrophage colony-stimulating factor), as well as regulatory IL-10 [10, 11].

According to literature data [12, 13], not only $CD56^{bright}$ NK cells mediate immune regulatory functions. Thus, the association of CMV-induced expansion of $NKG2C^{+}$ NK cells with a lower risk of disability progression in MS was described, suggesting the influence of these cells on the clinical course of the disease. $NKG2C^{+}$ human NK cells are part of the $CD56^{dim}$ population, which mediates cytotoxicity and cytokine production when interacting with target cells either directly or indirectly by antibody-dependent cellular cytotoxicity (in this case, the interaction of IgG with CD16A on NK cells).

According to a recent study by Ding et al. [14], immunosuppressive therapy or MSDMM therapy lead to a significant increase in the ratio of $CD56^{dim}$ NK cells to circulating follicular T helper cells. This ratio made it possible to significantly differentiate patients with recurrent MS from healthy individuals and patients in remission. The authors assumed that this ratio may become a new predictor of disease activity and evaluation of treatment effectiveness.

In 2024, Dal et al. [15] showed that a lower relative content of NK cells three months after anti-CD20 therapy (rituximab and ocrelizumab) correlates with the presence of disease activity six months after therapy, which corresponds to the possible protective role of NK cells in MS. Also, compared with the baseline values, anti-CD20 antibody therapy led to an absolute and relative decrease in B-lymphocyte levels and an increase in absolute and relative NK cell levels three and five months after therapy.

### Control mechanisms of cross-activated immune cells to Epstein-Barr virus antigens

In healthy donors with antibodies to the nuclear antigen of the Epstein-Barr virus ($EBNA_{386–405}$) and in patients with MS, their cross-reactivity against the myelin sheath antigen $GlialCAM_{370–389}$ (glial cell adhesion molecule) has been shown. Moreover, this cross-reactivity is capable of eliciting an immune response in both MS patients and healthy donors [9, 16].

In this regard, Vietzen et al. conducted an extensive search for differences in the immune response to EBV antigens in MS patients and healthy donors. The cohorts of 270 EBNA-1 seropositive MS patients and 270 EBNA-1 seropositive healthy donors were analyzed, compared by sex, age, and time since seroconversion to EBV antigens and the onset of infectious mononucleosis. All MS patients had high levels of antibodies to $EBNA_{386–405}$. Among the group of healthy donors, some had low levels of antibodies to $EBNA_{386–405}$ ($EBNA^{low}$ group, 162 people), while some had high levels ($EBNA^{high}$ group, 108 people). It is noteworthy that both MS patients and healthy $EBNA^{high}$ donors showed significantly higher levels of $EBNA_{386–405}$-specific immune cells, in particular plasma $CD4^{+}$T cells and $CD8^{+}$T cells, compared to the $EBNA^{low}$ group [17]. Thus, healthy donors from the $EBNA^{high}$ group also have immunological prerequisites for autoimmune damage to the myelin sheath. However, this does not happen, probably due to the presence of protective factors that prevent an autoimmune response.

The results of Vietzen et al. suggest that one of the important factors preventing MS development consists in the destruction of autoimmune $GlialCAM_{370–389}$-specific cells by cytotoxic NK cell reactions. At the same time, in patients with MS, the effectiveness of this process is reduced. Thus, this study revealed a number of differences between the group of MS patients with antibodies to $GlialCAM_{370–389}$ and healthy EBV carriers who also have antibodies to $GlialCAM_{370–389}$. In particular, healthy EBV carriers with autoantibodies to $GlialCAM_{370–389}$ showed a significantly higher representation of NK cells of the $NKG2D^{+}$ type ($NKG2D^{+}$ NK cells) with a highly active homozygous genotype — $NKG2D^{HNK/HNK}$. In the population of healthy carriers of autoantibodies to $GlialCAM_{370–389}$, the rate of highly active $NKG2D^{+}$ NK cells was about five times higher than in that of carriers of autoantibodies to $GlialCAM_{370–389}$ suffering from MS. The level of $NKG2C^{+}$ NK cells in the control groups was also significantly higher than in patients with MS [17].

In MS patients, autoreactive cells are likely to avoid regulatory and cytotoxic immune reactions effectively by inhibiting NK cells. One of the mechanisms behind this inhibition is an increase in the presence of HLA-E on the surface of B cells, which is induced by certain types of EBV. Normally, HLA-E, bound to normal peptides from HLA class I, signals NK cells that the cell has not been altered and does not need to be eliminated [18]. However, in MS, this mechanism

can become overly active, preventing NK-mediated elimination of autoreactive B cells. HLA-E can play an important role in the immune evasion of EBV-infected cells from natural killers: binding of HLA-E to NKG2A$^+$ on NK cells is known to inhibit their function [19].

HLA-E is stabilized by a peptide derived from the Epstein-Barr virus latent membrane protein 1 (LMP-1), expressed in latently infected EBV cells [20]. LMP-1 is a polymorphic peptide: different variants of EBV may have different variants of LMP-1. It was found that certain variants of LMP-1 (GGDPHLPTL and GGDPPLPTL) led to a stable increase in the level of HLA-E on the surface of B cells specific to $GlialCAM_{370-389}$. It has been shown that almost all MS patients are carriers of the above-mentioned EBV variants that increase HLA-E expression. Increased EBV reactivation and subsequent IL-27 expression correlate with increased HLA-E expression and inhibition of NKG2A$^+$ effector cells in MS patients [17]. IL-27 is a member of the IL-12 family, which is important in the pathogenesis of autoimmune disorders [21]. The NKG2A receptor is one of the inhibitory receptors of NK cells [22].

According to Vietzen et al., the factors associated with a high risk of MS in EBV carriers comprise a low or absent NKG2C$^+$ NK cell response (OR 41.3), variants GGDPHLPTL and GGDPPLPTL of the LMP-1 peptide in EBV (OR 39.6), a low-active $NKG2D^{LNK}$ genotype (OR 8.9) and HLA-E*01:01 (OR 4.3). At the same time, the combination of three or more risk factors leads to an increased risk of MS in carriers of autoreactive antibodies to the EBV nuclear antigen by about 180 times. In addition, infection with EBV with the risky LMP variant in combination with the HLA-E*01:01 genotype increases the risk of developing MS by about 260 times [17]. The importance of NK cells in the removal of autoreactive cells has been confirmed in other studies. It is worth noting that the data on the role of a certain decrease in NK activity in the MS pathogenesis are consistent with the understanding of psychoemotional stress being one of the most important risk factors in the MS etiology. The NK cell function is particularly impaired by psychoemotional stress [23, 24].

## Prospects for add-on MS therapy aimed at controlling Epstein-Barr virus-induced immune cross-reactions

In connection with the description of possible immunological mechanisms that ensure protection against MS development in the presence of autoantibodies to CNS antigens, it appears relevant to analyze possible prevention and therapy options aimed at strengthening these mechanisms. These options can be broadly divided into those aimed at enhancing immune regulatory reactions that ensure the autoreactive cells removal, as well as those aimed directly at reducing the EBV level in the body. Further, we will consider the properties of a number of medications offered as an additional MS therapy from these standpoints.

## Possibilities for reducing the presence of EBV in the body

EBV infection plays a central role in terms of triggering disruption of immune tolerance mechanisms. However, to date, antiviral medications or vaccines for the treatment and prevention of this infection have not yet been developed. Therefore, it seems promising to search for various compounds aimed at controlling EBV-induced immune cross-reactions. Regarding possible medications for add-on MS therapy with a favorable safety profile, it is of interest that various compounds of natural origin, especially polyphenols and terpenoids such as curcumin, epigallocatechin gallate, resveratrol, moronic acid and andrografolide, exhibit antiviral activity against EBV [25].

Some biologically active compounds isolated from medicinal plants inhibit the early stages of EBV infection. Quercetin, a polyphenolic compound isolated, in particular, from licorice root, prevents the recognition of EBV receptors and, consequently, blocks the penetration of EBV into cells [26]. Another study showed the ability of quercetin to suppress the expression of EBNA-1 and LMP-2, which may help reduce cross-reactions to EBV antigens [27].

A significant antiviral effect of curcumin has been shown, in particular against herpes simplex type 1 and type 2 viruses, CMV, Kaposi's sarcoma-associated herpesvirus, EBV, and bovine herpesvirus 1. The mechanisms of antiviral effects of curcumin are related to its ability to interfere with a number of cellular and molecular processes that are necessary for the expression and replication of viral genes. Curcumin (10 μM) increases the proportion of the plasma membrane accepting the conformation of the lipid raft, which confirms the evidence that curcumin can modulate the lipid bilayer [28]. Lipid rafts are dynamic ensembles of proteins and lipids that float freely in the liquid disordered bilayer of cell membranes, being also capable of agglomerating into large ordered platforms. These structures are important for regulating various membrane functions in eukaryotic cells [29]. Curcumin suppresses the proliferation of human nasopharyngeal carcinoma cells associated with EBV by inhibiting the expression of nuclear antigen 1 of the Epstein-Barr virus. Thus, the 50% inhibitory concentrations of curcumin were 12.4 μM and 3.3 μM for 24-h and 48-h curcumin treatment, respectively [30].

It is worth noting that the above compounds exhibit antiviral activity in in vitro studies in relatively high concentrations: as a rule, several μM/L or more, which is many times higher than their plasma concentrations. In recent years, a number of clinical reports have appeared on ways to increase the bioavailability of lipophilic compounds, such as the use of various nanoforms, liposomal forms, micellar forms, as well as combinations of various substances. In particular, the use of micellar forms of curcumin has made it possible to achieve plasma levels of this compound comparable to its concentrations in in vitro studies [31, 32].

## Medications aimed at enhancing immune responses that ensure the removal of autoreactive cells

As noted above, protection against the development of MS in individuals with autoreactive antibodies is largely mediated by the activation of the effector link of immunity against autoreactive cells. This includes certain subpopulations of NK cells and CD8$^+$T cells. Agents with a mild immune stimulating effect may be promising for enhancing immune regulatory reactions that ensure the removal of

autoreactive cells. Thus, the effect of a number of MSDMM is associated with increased NK activity. In particular, in patients receiving dimethyl fumarate (MSDMM 1st line), the total number of lymphocytes decreased depending on the time of exposure. The number of NK cells showed a heterogeneous trend, eventually increasing by about 86% following two years of treatment [33]. However, it should be noted that the use of highly active agents for the purpose of immunomodulation and increased NK activity, such as antibody therapy, may be associated with a number of side effects. The latter may result in cessation of the use of already approved agents [34].

The medications with a favorable safety profile, having immunotropic and neuroprotective effects and suitable for additional therapy of MS, include compounds capable of exhibiting an immune stimulating effect. Thus, urolitin A (a polyphenolic metabolite of the intestinal microbiota) not only has an anti-inflammatory effect against chronic inflammation, but also enhances the persistence and effector functions of $CD8^+$ cytotoxic T lymphocytes, as well as the activity of NK cells [35–37].

Quercetin, the abovementioned polyphenol, increased the proportion of NK cells in in vivo experiments when administered to mice at a dose of 1 mg/kg every 2 days for 30 days without affecting the populations of T and B cells. Also, due to binding to the MYH9 protein (the main component of the cytoskeleton, which plays an important role in the preservation and maintenance of the functionality of hematopoietic stem cells), this polyphenol increased the number and stimulated the maturation of NK cells [38]. However, there are studies where taking polyphenols did not have a significant effect on NK activity. Thus, taking 500–1000 mg of quercetin had no significant effect on NK cell activity in healthy adult women [39]. Perhaps similar results may be related to the previously mentioned low bioavailability of polyphenols.

Quercetin, like many other polyphenols, is found in various products of natural origin (such as grape seeds, onions, garlic, tea, and others). For example, fresh onions contain about 30-45 mg/100 g of quercetin and 4.5 mg/100 g of kaempferol [40]. Due to the low bioavailability of polyphenols, as already noted above, it may be promising to use their combinations with other substances capable of increasing their total bioavailability. From this point of view, the use of natural extracts containing a range of active substances can be effective in enhancing the resulting bioavailability. Thus, the ability of various plant extracts to enhance the activity of NK cells has been shown [41].

According to the results of a recent randomized, double-blind, placebo-controlled trial, the use of onion peel extract (1000 mg of extract per day for 8 weeks) improves NK cell activity in patients with moderate symptoms of upper respiratory tract diseases without any significant side effects [42]. These clinical results are consistent with those obtained in vitro, according to which incubation of peripheral blood mononuclear cells (PBMC) with onion extracts (*Allium cepa*) led to a significant increase in the rate of $CD16^+$ NK cells [43]. Oral administration of a combined extract of *Sargassum coreanum* (at dosages of 30 mg/kg, 100 mg/kg or 300 mg/kg for 4 weeks) and *Curcuma longa* (5 mg/kg, 4 weeks) to rats also caused an increase in NK cell activity [44].

Focaccetti et al. obtained promising results from an in vitro use of a combination of curcumin and resveratrol. In a human PBMC culture, the combination of these polyphenols (at concentrations of 5 μM), on the one hand, increased the production of IL-10 by regulatory T cells. On the other hand, this combination enhanced the activity of NK cells by increasing and decreasing the regulation of activating and inhibitory receptors, respectively, as well as increasing the level of CD68 expression on monocytes/macrophages [45].

The use of curcumin as an add-on MS therapy is being actively studied, including via clinical trials. To date, a number of clinical studies have reported the efficacy of an add-on curcumin MS therapy, especially when using forms with increased bioavailability [46-48].

Alloferon, an antimicrobial cytokine-like peptide, is also capable of stimulating NK activity and increasing NKG2D production in NK cells, while possessing anti-inflammatory properties. This renders alloferon a promising research object for add-on MS therapy [49, 50].

## CONCLUSION

The results obtained in recent years indicate the important role of the immune response to EBV in the etiology and pathogenesis of MS. It seems likely that the removal of autoreactive cells, cross-reactive to EBV antigens, using cytotoxic $CD8^+$ T cells, and NK cells in particular, is one of the main mechanisms preventing the development of autoimmune CNS lesions in MS. A number of risk factors associated with the immune response to EBV have been identified, which may increase the likelihood of developing MS. These risk factors include the following: low or absent $NKG2C^+$ NK cell response, variants GGDPHLPTL and GGDPPLPTL of the LMP-1 peptide in EBV, low-activity genotype $NKG2D^{LNK}$ and HLA-E*01:01. These findings create opportunities for the emergence of new approaches to the prevention and treatment of MS. Thus, the use of certain components of the immune response to EBV, such as NK cell activity, may be promising as a therapeutic target.

Agents with a favorable safety profile for add-on MS therapy may be suitable for these purposes. The efficacy of these medications, especially those of natural origin, may be due to a combination of antiviral, anti-inflammatory, and immune-stimulating activities aimed at enhancing immunological mechanisms capable of eliminating autoreactive cells.

Many of these products are characterized by low bioavailability, which can be enhanced by modern biotechnological methods, e.g., creation of micellar molds. At the same time, the introduction of such tools into clinical practice is hampered by the lack of respective clinical data. Further comprehensive clinical studies of complementary MS therapies are needed, both in combination with classical MSDMM and as monotherapy in patients who, for various reasons, receive no specific pathogenetic therapy.

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