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ПАРАМЕТРЫ КЛЕТОЧНОГО ИММУНИТЕТА У БОЛЬНЫХ РЕМИТТИРУЮЩЕЙ ФОРМОЙ РАССЕЯННОГО СКЛЕРОЗА

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Резюме. Целью настоящей работы стало изучение некоторых параметров клеточного иммунитета у больных рассеянным склерозом (РС). В исследование были включены 10 пациентов с ремиттирующей формой РС в возрасте от 32 до 50 лет. Диагноз был установлен клинически и подтвержден магнитно-резонансным исследованием. Пациенты не получали иммуносупрессивную терапию в течение по крайней мере 6 месяцев до начала исследования. Неврологический статус всех обследованных пациентов оценивался по функциональной шкале Куртцке с использованием расширенной шкалы инвалидизации (EDSS) и составил в среднем 4,0±0,67 балла. Среднее число обострений в год было 1,25±0,25. При исследовании таких параметров иммунного статуса, как количество Т-, В-, NK-клеток, содержание иммуноглобулинов, фагоцитарная активность моноцитов и гранулоцитов, продукция ими активных видов кислорода, у пациентов с РС существенных различий в сравнении с нормальным донорским уровнем не наблюдалось. Вместе с тем, нами было отмечено усиление пролиферативного ответа мононуклеарных клеток крови на миелиновый антиген в 2,35 раза. Содержание $CD4^+CD45RO^+CD62L^+$ и $CD8^+CD45RO^+CD62L^+$ центральных Т-клеток памяти, а также $CD8^+CD45RO^+CD62L^-$ эффекторных Т-клеток памяти в крови больных РС значимо превышало контрольные значения ($p < 0,05$). Также у больных РС, по сравнению со здоровыми лицами, имело место повышенное содержание наивных $CD4^+CD45RO^-$ и $CD8^+CD45RO^-$Т-клеток, несущих IFNγ ($p < 0,01$), и увеличение $CD4^+CD45RO^+$ и $CD8^+CD45RO^+$Т-клеток памяти, продуцирующих в ответ на активацию IFNγ или IFNγ вместе с IL-4 ($p < 0,01$). С этими данными согласуется значительное увеличение сывороточных уровней IFNγ и IL-17 и отсутствие изменений уровня IL-4. Относительное содержание «наивных» $CD4^+CD25^+FoxP3^+$, а также индуцированных $CD4^+CD25^-FoxP3^+$ регуляторных Т-клеток у больных РС существенно не изменялось по сравнению с донорскими значениями. Результаты оценки некоторых показателей иммунного статуса у больных РС свидетельствуют о функциональной перестройке иммунной системы в сторону Th1 типа иммунного ответа. Очевидно, что иммунотропное лечение РС должно быть направлено на инактивацию аутоиммунных Т- и В-лимфоцитов, подавление продукции провоспалительных медиаторов и усиление активности естественных и индуцированных регуляторных Т-клеток.

Ключевые слова: клеточный иммунитет, Т-лимфоциты, цитокины, клетки памяти, рассеянный склероз, Т-клеточная вакцина

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CELLULAR IMMUNITY PARAMETERS IN PATIENTS WITH REMITTING MULTIPLE SCLEROSIS

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Abstract. The aim of this work was to study some parameters of cellular immunity in patients with multiple sclerosis (MS). The study included 10 patients with relapsing-remitting MS aged 32 to 50 years. Diagnosis was clinically established and confirmed by magnetic resonance imaging. Patients did not receive immunosuppressive therapy for at least 6 months prior to study entry. The neurological status of all examined patients was assessed using the Kurtzke functional scale using the Extended Disability Scale (EDSS) and averaged 4.0±0.67 points, the mean number of exacerbations per year was 1.25±0.25. While studying such parameters of the immune status such as the number of T, B, NK-cells, the content of immunoglobulins, the phagocytic activity of monocytes and granulocytes, their production of reactive oxygen species, no significant differences were observed in patients with MS in comparison with the normal donor level. At the same time, we have noted an increase in the proliferative response of mononuclear blood cells to myelin antigen by 2.35 times. The content of $CD4^+CD45RO^+CD62L^+$ and $CD8^+CD45RO^+CD62L^+$ central memory T-cells, as well as $CD8^+CD45RO^+CD62L^-$ effector memory T-cells in the blood of MS patients significantly exceeded the control values ($p < 0.05$). Also, in MS patients, compared with healthy individuals, there was an increased level of naive IFNγ-positive $CD4^+CD45RO^-$ and $CD8^+CD45RO^-$T-cells ($p < 0.01$), and an increase in $CD4^+CD45RO^+$ and $CD8^+CD45RO^+$ memory T-cells producing IFNγ or IFNγ together with IL-4 in response to the activation ($p < 0.01$). Consistent with these data, there were significantly increased serum IFNγ and IL-17 levels and no changes in IL-4 levels. The relative level of naive $CD4^+CD25^+FoxP3^+$, as well as induced $CD4^+CD25^-FoxP3^+$ regulatory T-cells in MS patients did not significantly change compared to donor values. The results of assessing some parameters of the immune status in MS patients indicate a functional reshaping of the immune system towards the Th1 type of immune response. It is obvious that immunotropic treatment of MS should be aimed at inactivating auto-immune T- and B-lymphocytes, suppressing the production of proinflammatory mediators, and enhancing the activity of natural and induced regulatory T-cells.

Keywords: cellular immunity, T-cells, cytokines, memory cells, multiple sclerosis, T-cell vaccine

Introduction

Multiple sclerosis is a neurodegenerative disease with an autoimmune pathogenesis. In 90% of cases, disease onset proceeds in a remitting form, so that each exacerbation aggravates severity of neurological symptoms. Over time, multiple sclerosis acquires a secondary progressive course in about 50% of cases. Primary progressive disease course occurs in about 10% of patients.

A great number of experimental and clinical studies were dedicated to MS pathogenesis and treatment and indicate that immune system plays a dominant role in its pathogenesis. [1]. The ability of the human immune system to respond to vast array of antigens poses a risk that some T-cells might recognize host own antigens, such as myelin antigens of the central nervous system (CNS). Most autoreactive T-lymphocytes are eliminated in the thymus via negative selection (central tolerance). However, some of these T-cells escape from thymus to peripheral sites usually being controlled by peripheral tolerance mechanisms. If case such mechanisms fail it might be due to weakened regulatory T-cells activity and/or increased effector T and B-cell resistance to suppression, autoreactive T-cells may be activated and become a sufficient cause for developing autoimmune disease [1, 5]. It was shown, that CNS in MS patients was infiltrated by activated T-cells, B-cells, plasma cells, dendritic cells and macrophages suggesting that both cellular and humoral immune responses, as well as various immunopathological effector mechanisms contribute to tissue damage. Type 1 $CD4^+$-helper T (Th1) cells produce cytokines (IFNγ, TNFα, IL-2) resulting in recruitment of resident macrophages and effector cytotoxic cells to inflammation site, secretion of proinflammatory cytokines, enhanced activity of antigen-presenting cells, as well as increased production of reactive oxygen and nitrogen species creating favourable conditions for developing inflammation [8]. Type 17 $CD4^+$-helper T-cells (Th17), producing IL-17 and IL-22, increase permeability of blood-brain barrier, activate myelin-reactive T- and B-cells. In addition

to releasing proinflammatory mediators, $CD8^+$T-cells directly attack oligodendrocytes and neurons, causing their death through secreted granzymes and perforin involved in pore formation and triggering programmed cell death [1]. This process leads to loss of myelin and damage to axons. It should be noted that entry of epitopes into the bloodstream may lead to a broader autoimmune response involving additional autoantigens [4, 6, 10].

Modern methods of treatment for multiple sclerosis are based on long-term immunosuppressants and disease-modifying drugs, which lower rate of relapses and severity of inflammation in the central nervous system. They decrease activity of B and T-cells as well as blood-brain barrier permeability. Obviously, it is also necessary to develop approaches for specific disease suppression not associated with systemic suppression of the immune system, but selectively suppressed immune responses to host own antigens [14]. The aim of this study was to examine some parameters of cellular immunity in patients with multiple sclerosis in order to search for and develop new methods of specific therapy and assess efficacy.

Materials and methods

The study was carried out within the framework of the Exploratory Scientific Research, approved by the Scientific Council and the Ethics Committee of the Federal State Budgetary Scientific Institution Research Institute of Fundamental and Clinical Immunology, Novosibirsk. The study included 10 patients with relapsing-remitting MS aged 32 to 50 years. Informed consent was obtained from each patient. The diagnosis was made clinically and confirmed by magnetic resonance imaging. Patients received no immunosuppressive therapy for at least 6 months prior to study entry. The neurological status of all examined patients was assessed using the Kurtzke functional scale, the Extended Disability Scale (EDSS) that averaged 4.0±0.67 points, the average annual number of exacerbations was 1.25±0.25. The immune status of patients (count of $CD4^+CD3^+CD45^+$ and $CD8^+CD3^+CD45^+$T-cells, $CD16^+CD56^+CD45^+$NK-cells, $CD19^+CD45^+$B-lymphocytes, serum immunoglobulins, phagocytic tests) was assessed in the clinical and immunological laboratory of the Institute by using standard methods.

To assess the antigen-induced proliferative response, PBMC were cultured in a 96-well plate at a concentration of 2×10^5 cells in complete culture medium RPMI 1640, with/without myelin basic protein (MBP) for 5 days in a humid atmosphere with 5% CO_2. Cell proliferation was evaluated by [^{3}H] thymidine incorporation.

The relative number of memory cells was determined by flow cytofluorimetry using phycoerythrin (PE)-labeled monoclonal antibodies (MA) LT4 (CD4) and LT8 (CD8) (Sorbent, Moscow) conjugated with fluorescein isothiocyanate (FITC) MA to CD45RO (EBioscience, USA) labeled with allophycocyanin (APC) anti-CD62L MA (eBioscience, USA). The following cell populations were determined based on surface marker staining: naive cells ($CD45RO^-CD62L^+$), central memory cells ($CD45RO^+CD62L^+$), effector memory cells ($CD45RO^+CD62L^-$). The data are depicted as the percentage of each population out of total lymphocyte count.

Surface markers of regulatory ($CD4^+CD25^+FoxP3^+$) cells were determined by using anti-CD4 MA labeled with APC; MA to IL-2 receptor (CD25) conjugated to FITC. FoxP3 expression was assessed by using PE-labeled MA (all reagents purchased from Becton Dickinson, USA). The percentage of positive cells was determined on a FACS Calibur immunocytometer.

The level of IFNγ and IL-4-producing lymphocytes was assessed by an intra-cellular cytokine staining in 4-hour PBMC cultures treated with 30 ng/ml phorbol ester, 1 μg/ml ionomycin, and 1 μg/ml brefeldin A (all ICN reagents, USA). After cultivation, the cells were treated with MA against surface markers CD4 and CD8 labeled with peridinine chlorophyll protein (PerCP) and conjugated with APC MA to CD45RO (eBioscience, USA), fixed, permeabilized and incubated with MA against IFNγ (FITC) and IL-4 (PE) (Becton Dickinson, USA). Next, the cells were washed and analyzed on a FACSCalibur™ flow cytometer (BD Biosciences, USA). Data are presented as the percentage of each cell population out of total lymphocyte count.

Serum cytokines IFNγ, IL-4, IL-17 were quantified by using the enzyme-linked immunosorbent assay using commercial kits (Vector-Best, Russia).

Results and discussion

We investigated parameters of immune status in MS patients and observed no significant differences compared to volunteers. T, B, NK-cell count, immunoglobulin level, phagocytic activity of monocytes and granulocytes as well as production of reactive oxygen species were within normal range (Table 1).

We noted proliferative response of MNCs to myelin antigen that increased by 2.35-fold, which may indicate at increased number or functional activity of myelin-reactive lymphocytes in patient blood samples.

The number of blood $CD4^+CD45RO^+CD62L^+$ and $CD8^+CD45RO^+CD62L^+$ central memory T-cells in MS patients, as well as $CD8^+CD45RO^+CD62L^-$ effector memory T-cells were increased significantly. Control values ($p < 0.05$). Our studies indicate at accelerated differentiation of naive cells into central $CD4^+$ and $CD8^+$ memory T-cells and cytotoxic effector $CD8^+$T-cells in MS. This effect promotes

TABLE 1. IMMUNOLOGICAL CHARACTERISTICS IN PATIENTS WITH REMITTING MULTIPLE SCLEROSIS, M±m

Immunological parameters	MS Patients
$CD4^+CD3^+CD45^+$T-cells, percentage of total lymphocytes	49.75±4.29
$CD8^+CD3^+CD45^+$T-cells, percentage of total lymphocytes	29.75±4.02
$CD16^+CD56^+CD45^+$NK-cells, percentage of total lymphocytes	7.00±0.91
$CD19^+CD45^+$B-lymphocytes, percentage of total lymphocytes	8.50±0.64
IgM serum	2.34±0.48
IgA serum	2.16±0.58
IgG serum	10.93±0.60
CIC level of circulating immune complexes in serum	27.50±10.04
Monocytes phagocytic, %	90.25±4.50
Granulocytes phagocytic, %	93.50±3.27
Monocytes producing reactive oxygen species, %	76.25±4.80
Granulocytes producing reactive oxygen species, %	91.25±3.12
Proliferative response of MNC from patients, cpm **medium** **mielin**	 2306±466 5416±965
Serum cytokine content **IFNγ, pg/ml** **IL-4, pg/ml** **IL-17, pg/ml**	 144.0±46.7 11.70±2.98 8.3±3.7
Memory T-cells **$CD4^+CD45RO^+CD62L^+$** **$CD4^+CD45RO^+CD62L^-$** **$CD4^+CD45RO^-CD62L^+$** **$CD8^+CD45RO^+CD62L^+$** **$CD8^+CD45RO^+CD62L^-$** **$CD8^+CD45RO^-CD62L^+$**	 4.89±0.56 7.64±1.38 6.55±0.54 0.37±0.10 1.28±0.30 4.67±1.37
Memory T-cells producing intracellular IFNγ и IL-4 **$CD4^+/CD45RO^+/IFN\gamma^+/IL\text{-}4^-$** **$CD4^+/CD45RO^+/IFN\gamma^-/IL\text{-}4^+$** **$CD4^+/CD45RO^+/IFN\gamma^+/IL\text{-}4^+$** **$CD4^+/CD45RO^-/IFN\gamma^+/IL\text{-}4^-$** **$CD4^+/CD45RO^-/IFN\gamma^-/IL\text{-}4^+$** **$CD4^+/CD45RO^-/IFN\gamma^+/IL\text{-}4^+$** **$CD8^+/CD45RO^+/IFN\gamma^+/IL\text{-}4^-$** **$CD8^+/CD45RO^+/IFN\gamma^-/IL\text{-}4^+$** **$CD8^+/CD45RO^+/IFN\gamma^+/IL\text{-}4^+$** **$CD8^+/CD45RO^-/IFN\gamma^+/IL\text{-}4^-$** **$CD8^+/CD45RO^-/IFN\gamma^-/IL\text{-}4^+$** **$CD8^+/CD45RO^-/IFN\gamma^+/IL\text{-}4^+$**	 8.60±3.64 2.68±1.09 8.69±4.91 1.93±0.90 0.96±0.29 0.48±0.22 11.10±4.23 4.39±2.48 1.47±0.84 7.48±2.09 1.43±0.56 0.74±0.25

antigen-specific T-cell expansion in response to repeated, systemic antigen effects [12].

It is believed that IFNγ-producing T-cells contribute to developing MS, whereas IL-4 production by T-cells may have a neuroprotective effect [7, 13]. We assessed blood T-cell count capable of producing IFNγ and/or IL-4. The data are presented in the Table 1 indicating that count of naive $CD4^+CD45RO^-$ and $CD8^+CD45RO^-$T-cells carrying IFNγ ($p < 0.01$) and $CD4^+CD45RO^+$ and $CD8^+CD45RO^+$ memory T-cells, producing IFNγ with/without IL-4 activated in MS patients vs. healthy individuals was significantly increased ($p < 0.01$). It indicates at systemic skewing of T-cell function towards pro-inflammatory immune responses.

These data show consistently a significantly increased serum levels of IFNγ and IL-17 without affecting IL-4 levels, which also indicates a shift towards dominance of Th1 immune reaction, which is a prerequisite for triggering specific autoimmune response.

A body of evidence on relative number of regulatory T-cells showed that the count of naive $CD4^+CD25^+FoxP3^+$ (2.58±1.22), as well as induced $CD4^+$ $CD25^-FoxP3^+$ (14.13±5.89) T-cells in MS patients did not change significantly compared to donor values (2.72±1.08 and 17.4±5.9, respectively).

Assessing some parameters of T-cell immunity in patients with multiple sclerosis indicates a functionally skewed immune system towards Th1 type immune response. It is believed that autoimmune T-helper (Th)-1 and Th17-cells specific for myelin-associated antigens play a major role in MS pathogenesis, regardless of initial triggering event [11]. Activated encephalitogenic T-cells invade the CNS, and, by producing pro-inflammatory cytokine recruit macrophages, $CD8^+$T-cells and NK-cells in nervous tissue-destructive processes [7]. It is assumed that activation of $CD4^+$T-cells (including memory cells) is associated with MS exacerbation, whereas activation of $CD8^+$T-cells reflect systemic immunological dysregulation in MS patients [2, 12]. IFNγ, TNFα and perforin produced by $CD8^+$T-cells are involved in macrophages activation and maintenance of chronic inflammation as well as demyelinating process.

It is obvious that immunotropic treatment of MS should be aimed at inactivating auto-immune T and B lymphocytes, suppressing proinflammatory mediator production, and enhancing activity of natural and induced regulatory T-cells. One of the most promising approaches for pathogenetic treatment of multiple sclerosis is based on vaccination with inactivated autoimmune myelin-reactive T-lymphocytes. Such an immunization leads to generation of anticlonotypic cytolytic $CD8^+$T-cells specifically recognizing idiotypic T-cell receptor structures involved in the autoimmune process [9]. Moreover, T-cell vaccination causes the generation of anti-clonotypic and anti-ergotypic $CD4^+$T-cells, producing anti-inflammatory cytokines IL-4 and IL-10 in activated state, thus preventing the development of the tissue destructive process. Also, T-cell vaccination stimulates functional activity of regulatory $CD4^+CD25^+$T-cells, induces anti-ergo-typical T-cell response and production of anti-idiotypic antibodies [15]. In our institute (NIIFKI), there was developed a new two-stage technology for producing a T-cell vaccine (TCV): i) cultured antigen-specific selection of the patient T-cells, and ii) T-cell growth for propagating cell number via nonspecific stimulation. A final vaccine is dominated by the most autoreactive T-cells, since in the presence of a complex of neuronal antigens, these cells receive the peak growth advantages *in vitro*. It implies that anti-idiotypic immune response induced by the polyclonal T-cell vaccine should primarily target those antigen-reactive cells mostly involved in the pathological process. We believe that T-cell vaccination can produce tangible results, especially in the early stages of the disease.

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