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ENDOGENOUS RETROVIRUS HERV - E *λ 4-1* INFLUENCE ON IMMUNE CELLS FUNCTIONAL ACTIVITY IN MULTIPLE SCLEROSIS PATIENTS

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Purpose: a comparative study of the blood immune cells functional activity in multiple sclerosis patients associated with the human endogenous retrovirus HERV - E *λ 4-1* activation, as well as the immunomodulating properties of the homologous to a conservative region of hydrophobic transmembrane protein p15E 17 - amino acid synthetic oligopeptide.

Materials and methods. Human endogenous retrovirus HERV - E *λ 4-1env* gene expression was determined by the method of reverse transcriptase polymerase chain reaction. The spontaneous and mitogen-induced blood mononuclear cells proliferative activity of patients with a progredient course of disease, as well as blood mononuclear cells of central and peripheral organs of the immune system cells and of experimental animals when exposed to retroviral oligopeptide in culture was evaluated by the of tritium-labeled thymidine incorporation.

Results and discussion. We found that multiple sclerosis patients with activated retrovirus HERV - E *λ 4-1* are characterized by a higher blood immune cells functional activity compared with healthy donors, as well as in multiple sclerosis patients, in whose blood mononuclear cells the expression of this retrovirus was not detected. Synthetic 17 - amino acid oligopeptide, homologous to the conservative region of the hydrophobic transmembrane protein p15E of the HERV retrovirus - E *λ 4-1*, increased the functional activity of blood mononuclear cells of multiple sclerosis patients, as well as the immune system central and peripheral organs cells and blood mononuclear cells of experimental animals *in vivo*. This oligopeptide's effect was not genetically restricted.

Conclusion. Human endogenous retrovirus HERV - E *λ 4-1* sequence - specifically increases the immune cells functional activity in multiple sclerosis patients, which determines its role in the disease pathogenesis.

Keywords: multiple sclerosis, progredient course, human endogenous retrovirus HERV - E *λ 4-1*, retroviral oligopeptide, thymocytes, splenocytes, blood mononuclear cells, functional activity, genetic restriction.

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Introduction. Multiple sclerosis (MS) is a socially significant polyetiological autoimmune disease of the nervous system with immune-mediated damage to the brain gray and white matter as a result of the inflammatory foci with fibrosis and **gliosis** of the subarachnoid and intracortical regions and secondary neurodegeneration formation [5,7]. Clinically, MS is characterized by progressive neurological dysfunction, cognitive insufficiency and affective disorders [16]. The MS incidence is characterized by a unique geographic distribution, reflecting the significance in the etiology of genetic susceptibility, disturbances of the epigenetic mechanisms of the gene expression regulation, as well as extragenetic factors, in particular, the latitude gradient, with the disease prevalence in the regions near the North and South Poles [1,9,14].

Among the autoimmune inflammation triggers in the nervous system in MS, endogenous retroviruses (ER) are considered to be one of the most significant that can induce polyclonal activation of T lymphocytes [8]. These retroviruses are an integrated as a provirus form of exogenous and are a type of mobile genome elements - RNA retrotransposons, DNA sequences that make up to 8% of the human genome, distributed in more than 700,000 discrete loci [6].

In according to the modern classification, ERs are combined into 3 classes, represented by 50 families of 3173

sequences with a single genomic organization: they consist of the 4 retroviral genes, limited with 2 long terminal repeats that regulate their expression [15]. As often as not, the activity of retroelements in the human genome is repressed by both genetic and epigenetic mechanisms [12]. However, during the process of evolution, as a result of mutations and recombinations, some of them acquired pathogenic properties and the ability to replicate, to form the virion structure and to produce the viral proteins [11]. Some of the ERs are associated with the development of autoimmunity [1,10], as they are able to produce proteins with immunomodulating properties and to act as superantigens - to form antigenic epitopes by the molecular mimicry mechanism recognized by the immune system cells [4,10,13]. Inflammation and activation of the immune system are some of the factors that modulate ER transcription, since their promoter regions contain the binding sites for transcription factors involved in the oxidative stress response formation that inhibits deacetylase activity, stimulating histone acetylation and activation of ER expression [8]. ER RNA can be recognized by Toll-like receptors as pathogen-associated, which induces of type I interferon production involved in the formation of the pathological process in autoimmune diseases [17]. Considering the previously obtained data about the association of the class I HERV – E *λ 4–1* subgroup retrovirus (ER *λ 4–1*) with the course of MS, as well as its ability to replicate and produce proteins [10,18], the purpose of this study was a comparative investigation of the blood immune cells functional activity in patients with multiple sclerosis associated with ER*λ 4–1* activation, as well as the synthetic 17-amino acid oligopeptide homologous to the conserved region of its hydrophobic transmembrane *env* protein p15E immunomodulating properties.

Materials and methods. 32 patients with an established diagnosis of MS, with a progredient course of the disease and 16 conditionally healthy donors were included in the study. The study protocol was developed in accordance with the Helsinki Declaration of the World Medical Association "Ethical principles of the medical research with human participation conducting" with amendments in 2013, and the "Rules of Good Clinical Practice", approved by the Order of the Russian Federation Ministry of Health No. 200n, dated in 04/01/2016. The *env* gene expression of ER *λ 4-1* was determined by the reverse transcriptase polymerase chain reaction method, in accordance with the method described by us earlier in the paper [2]. The patient's blood mononuclear cells (MNCs) proliferative activity was assessed by the standard method of incorporating of H^3labeledthymidine into a 72 - hours cell culture, as we described in the paper [3]. The 17-amino acid retroviral or control (with reverse amino acid sequence) oligopeptides were introduced into the cell culture in 24 hours after the start of cultivation with the suboptimal concentrations of mitogens, also at suboptimal concentrations (50 μg/ml) determined in the preliminary experiments series [4].

The study of the immune cells functional activity *in vivo* was performed in healthy adult mice - male (CBAxC57Bl /6) F1, at 12 weeks of age, weighing of 18-20 g, obtained from the Scientific and E.D. Goldberg Research Institute of Physical and Radiotherapy Experimental Biological Clinic of Laboratory Animals, , TSRMC RAS, Tomsk. Experiments with animals were carried out in accordance with the order of the Russian Federation Ministry of Health and the Social Development No. 708n dated in August 23, 2010, "On approval of laboratory practice rules" and "Guidelines for experimental (preclinical) of new pharmacological substances researches" (Moscow, 2005). All manipulations complied in accordance with the rules adopted by the "European Convention for the Protection of Vertebrate Animals used in experiments or for other scientific purposes" (Strasbourg, 1986). Oligopeptides at a dose of 300 μg/mouse were administered intravenously for three times, with an interval of 48 hours. In 24 hours after the oligopeptides, third injection, the MNC, thymus and spleen proliferative activity was determined, as described above.

Statistical data processing. was performed with the using of descriptive statistics, comparative analysis methods, mediating the non-parametric Kruskal-Wallis H-test, Mann-Whitney U-test, using the Statistica 10.0 (StatSoft, USA) commercial software package. Results were presented as medians and intervals between the 1 and 4 quartiles (Me (25%; 75%). Differences were considered as statistically significant at $p < 0.05$.

Results and discussion. To assess the of ER *λ 4-1* effect on the of MS patients blood immune cells functional activity, in a series of preliminary experiments the presence of its activation in patients' MNC on the base of the assessment of its *env* gene expression responsible for the virus envelope synthesis and its exit out of the cell was investigated. For the further research, per the 16 samples of MNCs both groups were selected each with the presence or absence of this retrovirus activation in them. The results of the MS patients MNC proliferative activity evaluation in the presence or absence of ER *λ 4-1env*gene expression in them, as well as under the retroviral oligopeptide in vitro exposure are presented in the Table 1.

Table 1

Effect of retroviral oligopeptide on the blood mononuclear cells proliferative activity in multiple sclerosis patients (Me (25%; 75%))

Groups, impact	0.9% NaCl	Control oligopeptide	Retroviral oligopeptide
Donors intact	1425 (871; 2110)	1625 (920; 2120)	2787 (2355; 3441)*
Donors, ConA	20722 (19111; 23914)	20485 (16240; 23560)	32227 (29998; 33683)*
Donors, PWM	7973 (6460; 9105)	8259 (7542; 9980)	10124 (8347; 12647)
MS patients ER(-), intact	1847 (1121; 2324)	1971 (967; 2490)	3567 (2945; 3876)*
MS patients ER(-), ConA	18396 (15811; 23501)	19920(17831; 22911)	30772 (28859; 33267)*
MS patients ER(-), PWM	8218 (5638; 9456)	9631 (7623; 10118)	9265 (7719; 9967)
MS patients ER(+), intact	2421 (2125; 3230)#	2704 (2520; 3307)	4395 (3998; 4775)*.#
MS patients ER(+), ConA	15873(13923; 20657)#	16004 (15645; 21007)	26034 (19892; 29076)*.#
MS patients ER(+), PWM	5197 (4887; 6345)#	7857 (6378; 8935)	7527 (6365; 7841)#

Note: ER (-) – the lack of the ER λ 4-1env expression; ER (+) - the presence of the λ 4–1 env expression; ConA - concanavalin A; PWM - pokweed mitogen; n = 16 in each group;
* - $p<0.05$ (Kruskal-Wallis H-criterion) between the corresponding parameters under the influence of the control and retroviral oligopeptides;
# - $p<0.05$ (Kruskal-Wallis H-criterion) between the corresponding parameters in the donors and MS patients groups.

It was found that in patients whose MNC were not expressing the ER *λ 4-1 env*, the spontaneous lymphocyte proliferation level, as well as the response to B and T cell mitogens stimulation, did not differ from the conditionally healthy volunteers corresponding parameters. At the same time, there was initially a higher level of spontaneous MNC mitotic activity, but a lower response to B and T cell mitogens stimulation in the MNC of patients with ER *λ 4-1 env* gene expression, in comparison with the appropriate parameters in healthy volunteers or MS patients with the lack of ER λ*4-1 env* gene expression.

The control oligopeptide did not change the cell cultures proliferative activity. In healthy volunteers and in patients with the lack of ER *λ 4-1 env* gene expression, the effect of the retroviral oligopeptide infers in increasing of the spontaneous and ConA-stimulated proliferation level; the effect of retroviral oligopeptide in MS patients with activated ER *λ 4-1* resulted in an even greater increase in spontaneous proliferation and had a co-stimulatory effect on the enriched with T - lymphocytes as a result of mitogenic stimulation cell cultures mitotic activity, which is probably one of the aspects of the MS pathogenesis .

In order to study the retroviral oligopeptide immunomodulating properties at the whole organism level, as well as the presence of its action genetic restriction, we evaluated the peripheral blood immune cells, as well as the cells of immune system central and peripheral organs functional activity in experimental animals when the oligopeptide was administered in vivo. It was found that the level of spontaneous and ConA-stimulated proliferation of thymocytes, splenocytes and MNCs under the retroviral oligopeptide action exceeded that level in the control groups of animals, which indicates that this oligopeptide stimulates the various degrees of maturity T-lymphocytes mitotic activity and the absence of its action genetic restriction (Table 2).

At the same time, the studied oligopeptide did not affect the cell cultures enriched with B lymphocytes proliferation as a result of the pokeweed mitogen stimulation.

Conclusion. Thus, the MS patients with activated ER *λ 4-1* are characterized by higher blood immune cells functional activity compared with those of the healthy volunteers and MS patients, with the lack of ER *λ 4-1env* gene expression. The synthetic 17 - amino acid oligopeptide homologous to the human endogenous retrovirus *λ 4-1* hydrophobic transmembrane protein p15E conserved region, associated with the multiple sclerosis course, increases the of blood mononuclear cells functional activity of patients in vitro, as well as the proliferation of experimental animal's blood immune cells and the cells of central and peripheral organs of immune system *in vivo*. Therefore, the ER λ 4-1 has a sequence - specific, genetically unrestricted immunomodulating properties that determine the role of this endogenous retrovirus in the pathogenesis of multiple sclerosis.

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Table 2

The effect of retroviral oligopeptide on the of blood mononuclear cells, cells of the immune system central and peripheral organs proliferative activity in mice (CBA´C57BL / 6) F1 (Me (25%; 75%))

Groups, impact	Spontaneous proliferation (imp/min)	ConA – stimulated proliferation (imp/min)	PWM- – stimulated proliferation (imp/min)
1.Thymocytes			
0.9% NaCl	852 (556; 1271)	24647 (19881; 28993)	945(718; 1044)
Control oligopeptide	1043 (678; 1364)	25564 (20765; 29144)	1180(754; 1250)
Retroviral oligopeptide	1975 (1302;2483)*	33105 (27675; 36165)*	1263(843; 1911)
2.Splenocytes			
0.9% NaCl	2899 (2282; 3154)	45981(30845; 53850)	31928(22184; 36543)
Control oligopeptide	2995 (2751; 3598)	42428 (32967; 51278)	29771(20567; 33852)
Retroviral oligopeptide	4066 (3256;4328)*	74246 (68977;77034)*	32470(19160; 35767)
3.Blood mononuclear cells			
0.9% NaCl	3547 (2159; 3465)	50661(33283; 53887)	29548(18276; 34547)
Control oligopeptide	3633 (2918; 3912)	42014 (32545; 51338)	27453(20657; 34278)
Retroviral oligopeptide	49554 (3176;5134)*	61324 (58116;73491)*	26541(19947; 34595)

Note: ConA - concanavalin A; PWM - pokweed mitogen; n = 9 in each group;
* - p<0.05 (Mann-Whitney U-criterion)

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BIODEGRADABLE VASCULAR PATCHES: A COMPARATIVE DESCRIPTION OF PHYSICOMECHANICAL AND HEMOCOMPATIBLE PROPERTIES

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RGD-modification is a promising approach to improve biocompatibility of biodegradable vascular patches, potentially suitable for arteriotomy. Vascular patches are electrospun from the blend of polycaprolactone and polyhydroxybutyrate/valerate and modified with RGDK, AhRGD and c[RGDFK] peptides using 1.6-hexamethylene diamine or 4.7.10-trioxa-1.13-tridecanediamine linkers. Their mechanical properties and hemocompatibility are assessed. As the benchmark samples we used human internal mammary artery and xenopericardial KemPeriplas-Neo patches that are routinely used for carotid endarterectomy. Tensile properties of both polymer and biological samples differ from that of native human internal mammary artery. Tensile strength and Fmax of KemPeriplas-Neo patches are 4- and 16.7-times higher ($p < 0.05$). Both, RGD-modified and unmodified PHBV/PCL, demonstrate results similar to human internal mammary artery. Young's modulus of KemPeriplas-Neo patches corresponds to that of native vessels, whereas in polymer patches it exceeds 9 times that of the last ($p < 0.05$). RGD-modified PHBV/PCL patches and original PHBV/PCL patches demonstrate few lysed red blood cells and mild platelet aggregation than KemPeriplas-Neo patches, indicating a high biocompatibility of polymers and modifying agents used to make vascular patches.

Keywords: tissue engineering, biodegradable polymers, vascular patches, surface modification, RGD-peptides.

Introduction. High prevalence of internal carotid artery atherosclerosis and advanced diagnosis have resulted in an increase in the number of carotid endarterectomy performed annually [10]. Carotid stenosis is commonly treated with medical therapy, carotid endarterectomy (CEA), and stenting [13]. Despite recent advances and emergence of minimally invasive techniques, CEA remains the preferred method for treating patients with carotid stenosis.

Randomized controlled trials on the effectiveness of PTFE, Dacron and bovine pericardial patches have shown a similar rate of complications in the long-term period [3]. Thus, patches used in the routine clinical practice does not fully correspond to all needs of vascular surgery, that necessitates the development of new materials and approaches to the design of advanced vascular patches.

The emergence of regenerative medicine has opened new horizons for tissue engineering approaches in the development of bioresorbable materials activating the regenerative potential of the body to restore the damaged vessel walls [15]. Synthetic biodegradable polymers such as polylactic acid (PLA), polyglycolic acid (PGA), and polycaprolatone (PCL) are widely used for this purpose [2, 11].

Synthetic polymers may be combined with the natural ones to increase the biocompatibility of the resultant product. Several studies reported the development of tissue-engineered vascular patch made from PGA and coated with poly-4-hydroxybutyrate (poly-4-hydroxybutyrate, P-4-HB). Tissue-engineered pulmonary artery augmentation patches derived from autologous circulating EPC and bone marrow–derived MSC functioned in vivo for up to 6 weeks in the ovine model grossly resembled the structure of the native pulmonary artery [12].

Although cell seeding on a matrix increases its in situ remodeling rate, this approach is generally considered as time-consuming and expensive. Therefore, it seems relevant to develop a self-assembling biodegradable material able to independently populate cells in situ. Moreover, the rapid formation of endothelial monolayers on the inner surface of the patches requires options for its stimulation. Both physical and chemical modifications of the tissue-engineered matrix surfaces are known. They produce proangiogenic effects and contribute to the endothelial cell seeding from the blood flow and surrounding tissues [1, 5, 8]. Thus, new functional biocompatible patches ensuring the regeneration of the damaged vessel wall are of paramount importance.

The **aim** of our study was to develop biodegradable vascular patches modified by various RGD peptides, and to compare their mechanical properties and hemocompatibility with xenopericardial patches, routinely used in the clinical practice.

Material and Methods. Polymer matrices were electrospun from a polymer