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The effects of human umbilical cord-derived multipotent mesenchymal stromal cell transplantation in mice of different strains with an experimental model of parkinsonism

Labunets I.[1,2], Panteleymonova T.[1,2], Kyryk V.[1,2], Toporova O.[1,3], Pikus P.[1,3], Litoschenko Z.[1,2]

[1]*Institute of Genetic and Regenerative Medicine, M. D. Strazhesko National Scientific Center of Cardiology, Clinical and Regenerative Medicine, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine*
[2]*D. F. Chebotarev State Institute of Gerontology, National Academy of Medical Sciences of Ukraine, Kyiv, Ukraine*
[3]*Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine, Kyiv, Ukraine*

*Corresponding author's e-mail: irina_labunets@ukr.net

ABSTRACT

One of the promising directions of cell therapy for Parkinson's disease/parkinsonism is the transplantation of human umbilical cord-derived multipotent mesenchymal stromal/stem cells (hUC-MMSCs), the effectiveness of which may depend on the recipient's genotype.

***PURPOSE** – to compare the effect of transplanted hUC-MMSCs on behavior, number of T-lymphocytes and macrophages in the brain and lymphoid organs of mice of different strains with a toxin-induced model of parkinsonism.*

***METHODS.** Adult (6-7-month-old) male mice of FVB/N (haplotype H-2^q) and 129/Sv (haplotype H-2^b) strains were administered the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) at a dose of 30 mg/kg (control group), and after 7 days, hUC-MMSCs at a dose of 500,000 cells were transplanted into the tail vein. Behavioral reactions were assessed in the "open field", rigidity and rotarod tests. The relative content of T-lymphocytes and activated macrophages in the brain, as well as the weight of lymphoid organs were determined.*

***RESULTS.** Under the influence of MPTP, the number of rearings, hole-peeking, body length and step length decreased; the number of boluses increased in FVB/N and 129/Sv mice, and the number of crossed squares in the open field test also decreased in 129/Sv mice. In the brain of mice of both strains, the content of activated macrophages increased and, in FVB/N mice, the number of T-lymphocytes increased too. The thymus weight decreased in mice of both strains, while the spleen weight decreased only in 129/Sv mice. Under the influence of hUC-MMSCs, the motor activity improved mainly in FVB/N mice, while the emotional activity improved in 129/Sv mice. The manifestations of rigidity decreased in mice of both strains. The content of T-lymphocytes and activated macrophages in the brain of mice from both strains, as well as the thymus weight, corresponded to the values of intact animals. The transplantation of hUC-MMSCs contributed to the survival of FVB/N and 129/Sv mice with the MPTP-induced parkinsonism model.*

***CONCLUSION.** The manifestations of behavioral disorders, changes in the content of T-lymphocytes and activated macrophages in the brain, the weight of lymphoid organs in mice with the MPTP-induced model of parkinsonism, as well as the positive effects of transplanted hUC-MMSCs in such animals largely depend on their H-2 genotype (analogous to the HLA system in humans). The results can provide the basis for the development of personalized cell therapy for parkinsonism using hUC-MMSCs.*

***KEY WORDS:** human umbilical cord-derived multipotent mesenchymal stromal cells; parkinsonism; behavioral reactions; brain T-lymphocytes and macrophages; thymus; spleen*

Parkinson's disease (PD) is one of the most widespread chronic progressive neurodegenerative pathologies, in which motor, sensory, emotional, autonomic, and cognitive disorders of the central nervous system (CNS) develop [1]. Factors of neuroinflammation and oxidative stress are of great importance in the development of morphofunctional changes in PD/parkinsonism [2, 3]. In particular, the damaging effect of the activation products of microglia/macrophage cells and T-lymphocytes (pro-inflammatory cytokines IL-1β, TNF-α, IFN-γ, chemokines, free radicals, reactive oxygen species) on the structure and functioning of CNS neurons in this pathology has been shown [4].

Currently, the role of genetic factors in the development of neurodegenerative diseases is being actively studied. The link between the risk of their development, on the one hand, and the polymorphism of the major histocompatibility complex (HLA) genes, as well as the production features of some pro-inflammatory cytokines (TNF-α) and immunoglobulins, on the other hand, has been revealed [5, 6]. Mice of different inbred strains that differ in H-2 haplotype (an analogue of the human HLA system) can be a promising model object for studying such a relationship [7, 8]. Such mice have certain differences in immunoendocrine, metabolic, neurochemical parameters, response to regulatory, damaging and therapeutic factors [9, 10].

The transplantation of multipotent mesenchymal stromal/stem cells (MMSCs) of various tissue origin (bone marrow, adipose tissue, umbilical cord, etc.) deserves attention in the cell therapy of PD/parkinsonism [11, 12]. These cells are capable of multilineage differentiation, trophic effect on damaged organs and tissues, synthesis and secretion of neurotrophic factors, and also exhibit anti-inflammatory, antioxidant and immunomodulatory properties [13-16]. The biological properties of human umbilical cord-derived MMSCs (hUC-MMSCs) attract the special attention of researchers and clinicians [17, 18]. These cells show little immunogenicity, which allows them to be used for allogeneic transplantation. hUC-MMSCs proliferate well enough *in vitro*, are capable of transdifferentiation into cells of ectodermal origin and synthesis of IL-10, TGF-β [19-21]. Their immunosuppressive effect is greater than that of similar cells derived from adipose tissue and bone marrow [22].

There is data on the influence of the mouse H-2 haplotype not only on the biological properties of MMSCs of various tissue origin, but also on their regenerative effects after transplantation into organisms with some pathological processes [23-25]. However, the significance of genetic factors for the reaction of an organism with neurodegenerative pathology to hUC-MMSCs transplantation remains insufficiently studied.

THE PURPOSE is to compare the effect of transplanted hUC-MMSCs on behavior, number of T-lymphocytes and macrophages in the brain and lymphoid organs of mice of different strains with a toxin-induced model of parkinsonism.

MATERIALS AND METHODS

Animals. The experiments were performed on male FVB/N (haplotype H-2q, n = 31) and 129/Sv (haplotype H-2b, n = 31) adult mice aged 6-7 months from the nursery of the Institute of Genetic and Regenerative Medicine of the M. D. Strazhesko National Scientific Center of Cardiology, Clinical and Regenerative Medicine. Other authors and we have shown that such mice have certain differences in the functioning of the nervous system, the immune system (synthesis of cytokines, antibodies) and the endocrine system (adrenal glands), as well as reactions to the action of some harmful factors (viruses, toxins) [26-28]. Experimental animals were kept in standard vivarium conditions with a fixed 12:12 light regime and free access to food and water *ad libitum*.

Biological material for experiments was collected following the euthanasia of mice through decapitation under ether anesthesia during the morning hours (9:00-10:00). All studies with experimental animals were carried out in compliance with the Law of Ukraine "On Protection of Animals from Cruelty", "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986), as well as with the approval of the Ethics Committee of the Institute of Genetic and Regenerative Medicine.

Experimental models. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was used to reproduce the parkinsonism model in mice. After systemic administration into mice MPTP damages dopaminergic neurons of the midbrain substantia nigra and leads to motor disorders that resemble PD symptoms in humans [29]. In our experiment, MPTP (*Sigma*, USA) was administered to adult mice of both strains subcutaneously (in the neck area) once at a dose of 30 mg/kg. We found that the use of such a neurotoxin administration scheme makes it possible to reproduce the late stage of parkinsonism development in mice, in which significant damage to dopaminergic neurons of the substantia nigra of the brain is observed [27].

Isolation and cultivation of hUC-MMSCs. Cells were isolated using the explant method from the umbilical cords of newborns, as previously described [30]. A healthy woman, who delivered a boy at 39 weeks of gestation, signed an informed consent to provide material for scientific research. An inverted microscope DM IL (*Leica*, Germany) was used to assess the condition of cultures. The culture of cells obtained from umbilical cord tissue after the 2nd passage was morphologically homogeneous and contained mainly small mitotically active spindle-shaped cells. They expressed the marker antigens CD105, CD73 and CD90 on the surface, but did not express CD45 and CD34, and also differentiated into osteoblasts, adipocytes and chondrocytes *in vitro*, which meets the minimum criteria of MMSCs [30] (**Fig. 1**). Cell immunophenotyping was performed on a BD FACSAria cell sorter (*Becton Dickinson*, USA).

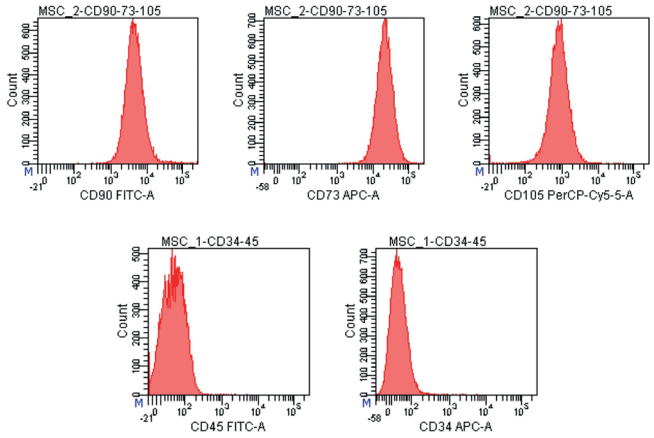

Fig. 1. Histograms illustrating the expression of surface markers (CD90, CD73, CD105, CD45, and CD34) on hUC-MMSCs, as determined by flow cytometry.

Native hUC-MMSCs of the 2nd passage were administered once into the tail vein of mice 7 days after the injection of MPTP at a dose of 500,000 cells in 50 μL of 0.9 % saline. Control group was injected with 0.9 % saline into the tail vein. The choice of the indicated term of hUC-MMSCs administration to mice is explained by the development of degenerative changes of neurons in the substantia nigra of mice 7 days after the administration of MPTP at a dose of 20 mg/kg [31].

Experimental groups. The mice were divided into 6 groups (**Table 1**). To except an individual response of the central nervous system to the neurotoxin in animals, behavioral tests were assessed before its administration. On the 22nd day of the experiment, mice of all groups were decapitated, the brain and lymphoid organs were isolated for research. Throughout the experiment, the number of surviving animals was recorded at intervals of 7, 14, and 22 days after the administration of MPTP.

Table 1. Distribution of animals in the experiment.

Groups	Number of mice	Experimental influences
1	9	Intact FVB/N mice
2	12	FVB/N mice injected with MPTP and, after 7 days, 0.9 % saline (control group)
3	10	FVB/N mice injected with MPTP and, after 7 days, hUC-MMSCs at a dose of 500,000 cells/mouse
4	9	Intact 129/Sv mice
5	12	129/Sv mice injected with MPTP and, after 7 days, 0.9 % saline (control group)
6	10	129/S mice injected with MPTP and, after 7 days, hUC-MMSCs at a dose of 500,000 cells/mouse

The functional state of the central nervous system was evaluated through behavioral reactions in the "open field", rigidity and rotarod tests. [27, 32, 33]. The "open field" test enables to assess in animals horizontal motor activity (number of crossed squares), orientation-exploratory activity (number of rearings and hole-peeking), emotional activity (number of fecal boluses). Mice of all groups were tested for 3 minutes.

The rotarod test, utilizing a rotating rod, allows for the assessment of coordination, muscle tone, and physical endurance. In the study, one of the test variations involved a gradual increase in the rotation speed of the shaft every 30 seconds, starting from 4 rpm at the 'start' and reaching 40 rpm [33]. The total time spent on the shaft (in seconds) and the critical (maximum) speed (in rpm) at which the animal either refused to move (hanged) or fell off the shaft were recorded.

Rigidity in mice was studied by body length and step length, as well as foot length and width (mm). The step length is one of the indicators of the change in the gait of animals, and its decrease indicates a violation of muscle function. Before assessing the gait of the animals, their feet were treated with non-toxic solutions of paints of different colors.

Immunophenotyping of brain cells for CD3, CD11b (Mac-1) markers was conducted using anti-mouse monoclonal antibodies conjugated with fluorochromes (*BD Bioscience*, USA): CD3-PE (Cat. no. 555275), CD11b-FITC (Cat. no. 557396). The working concentration of monoclonal antibodies was 0.5 μg/mL. 1×10^6 cells from brain homogenate in 50 μL of staining buffer (phosphate buffer supplemented with 1 % fetal bovine serum and 0.1 % sodium azide) were placed into 5 mL test tubes, and then monoclonal antibodies were added at a 1:50 dilution. Incubation was carried out for 20 min at a temperature of 4 °C, after which the cells were washed in CellWash buffer (*BD Bioscience*, USA), centrifuged at 200 ×g for 5 min at a temperature of 4 °C. Immediately before the analysis, the cell suspension was passed through 70 μm cell filter. Measurements were conducted on a BD FACSAria cell sorter (*Becton Dickinson*, USA) using the BD FACSDiva 6.1 software. At least 20,000 events were recorded for analysis.

The weight of lymphoid organs. The weight of the thymus and spleen (mg) was measured in the animals, and the values of the thymus and spleen indices (mg/g, 10^{-3}) were calculated based on the ratio of the weight of the examined organs to the body weight (g).

Statistical analysis of the results was performed using the Student's t-test. The difference between the indicators of the experimental groups was considered significant at a value of $p < 0.05$. Statistica 7.0 software (*StatSoft Inc*., USA) was used for statistical processing of the obtained data. The results were presented as the arithmetic mean and the error of the mean (M ± m).

RESULTS AND DISCUSSION

The effect of hUC-MMSC transplantation on the behavior of mice with a model of parkinsonism. It was observed that, in FVB/N mice, the administration of MPTP resulted in a significant decrease in the number of rearings, hole-peeking, body length, and step length, while the number of boluses increased significantly compared to intact animals. (**Table 2**). After the transplantation of hUC-MMSCs in such mice, the number of rearings and step length significantly increase compared to the control group (MPTP only); at the same time, the step length reaches the values of the indicator of the intact group of animals (**Table 2**). In mice of this strain, after the administration of hUC-MMSCs, the values of the rotarod test indicators become higher compared to the intact and control groups of animals (**Table 2**).

In 129/Sv mice, after the MPTP administration, there was a decrease in the number of crossed squares, rearings, hole-peeking, body length and step length, as well as an increase in the number of boluses compared to animals of the intact group (**Table 2**). After the transplantation of hUC-MMSCs in such mice, the number of boluses decreases, while body length and step length become higher than in the control group; at the same time, the body length indicator corresponds to the values of intact animals (**Table 2**). In 129/Sv mice, the indicators of the rotarod test did not significantly differ between the experimental groups.

Table 2. Behavioral indicators of experimental mice, M ± m.

Indicator	FVB/N mice			129/Sv mice		
	Intact (n = 9)	MPTP+ saline (control) (n = 6)	MPTP+ hUC-MMSCs (n = 7)	Intact (n = 9)	MPTP+ saline (control) (n = 6)	MPTP+ hUC-MMSCs (n = 10)
Number of crossings	81.2 ± 5.9	67.5 ± 6.0	74.7 ± 5.5	41.0 ± 4.3#	23.3 ± 2.5*#	21.0 ± 2.1*#
Number of rearings	3.25 ± 0.5	1.0 ± 0.1*	1.6 ± 0.2*&	1.5 ± 0.4#	0.3 ± 0.1*#	0.3 ± 0.1*#
Number of holes	4.0 ± 0.5	2.0 ± 0.2*	2.6 ± 0.3*	1.66 ± 0.3#	0.67 ± 0.2*#	0.45 ± 0.1*#
Number of fecal boluses	0.1 ± 0.01	0.7 ± 0.01*	0.6 ± 0.1*	1.8 ± 0.3#	2.66 ± 0.3*#	1.0 ± 0.2*&
Body length, mm	75.6 ± 1.8	70.0 ± 1.9*	65.8 ± 1.6*	91.0 ± 1.8#	82.0 ± 1.4*#	87.0 ± 1.4#&
Step length, mm	47.3 ± 1.3	42.0 ± 2.1*	49.3 ± 2.3&	52.0 ± 2.1	30.0 ± 1.8*#	46.0 ± 2.5*&
Foot length, mm	12.3 ± 0.6	13.0 ± 0.5	11.8 ± 0.4	12.8 ± 0.4	12.6 ± 0.4	12.8 ± 0.5
Foot width, mm	8.3 ± 0.2	8.0 ± 0.3	8.3 ± 0.2	8.2 ± 0.2	8.0 ± 0.1	8.2 ± 0.2
Rotarod, rpm	26.0 ± 2.2	31.3 ± 1.9	46.0 ± 1.7*&	27.2 ± 3.0	27.3 ± 5.0	32.4 ± 4.3
Rotarod, sec	175.0 ± 15.8	190.0 ± 14.6	300.0 ± 12.9*&	187.0 ± 22.7	160.0 ± 37.7	198.0 ± 32.2

*Note: * – $p < 0.05$ compared to the intact group; & – $p < 0.05$ compared to the control group (MPTP); # – $p < 0.05$ compared to FVB/N mice.*

Therefore, in FVB/N and 129/Sv mice, under the influence of neurotoxin MPTP, motor, exploratory and emotional activity is disturbed, and the signs of rigidity appear. The transplantation of hUC-MMSCs has a positive effect on the disturbed behavior of experimental mice of both strains; behavioral changes in such mice were both unidirectional and had strain features. Specifically, in FVB/N mice, the influence of cells led to increased motor activity and physical endurance, whereas 129/Sv mice exhibited a decrease in emotional activity and more pronounced changes in rigidity.

The effect of hUC-MMSCs transplantation on the content of T-lymphocytes and activated macrophages in the brain of mice with a model of parkinsonism. It was found that the proportion of $CD3^+$ and $CD3^+CD11b^+$ cells in the brain of FVB/N mice significantly increases after the administration of MPTP, while after the transplantation of hUC-MMSCs the value of these indicators decreases to the level of intact animals (**Table 3**).

In the brain of 129/Sv mice, the relative number of $CD3^+CD11b^+$ cells significantly increased compared to the values of intact animals and corresponds to their values after the hUC-MMSCs transplantation (**Table 3**).

Table 3. The content of T-lymphocytes and activated macrophages in the brain of experimental mice, M ± m.

Indicator	FVB/N mice			129/Sv mice		
	Intact (n = 9)	MPTP+ saline (control) (n = 6)	MPTP+ hUC-MMSCs (n = 7)	Intact (n = 9)	MPTP+ saline (control) (n = 6)	MPTP+ hUC-MMSCs (n = 10)
$CD3^+$, %	4.5 ± 0.2	5.6 ± 0.3*	4.03 ± 0.2&	2.85 ± 0.2#	2.55 ± 0.2#	2.56 ± 0.2#
$CD3^+CD11b^+$, %	0.35 ± 0.04	0.6 ± 0.06*	0.43 ± 0.05&	0.8 ± 0.07#	1.8 ± 0.1*#	0.78 ± 0.07#&

*Note: * – p < 0.05 compared to the intact group; & – p < 0.05 compared to the control group (MPTP); # – p < 0.05 compared to FVB/N mice.*

Therefore, under the influence of MPTP, the content of T-lymphocytes and activated macrophages increases in the brain of FVB/N and 129/Sv mice. At the same time, the content of both T-lymphocytes and activated macrophages significantly increases in FVB/N mice, whereas the changes in the content of only activated macrophages are observed in 129/Sv mice. In mice of both strains, after the transplantation of hUC-MMSCs, the content of T-lymphocytes and activated macrophages in the brain decreases to the values of intact groups.

The effect of hUC-MMSCs transplantation on lymphoid organs of mice with a model of parkinsonism. It was found that in FVB/N mice, after the administration of MPTP, the thymus weight decreases, while the spleen weight remains unchanged (**Table 4**). After the transplantation of hUC-MMSCs to mice of this strain, thymus weight did not differ from those of intact animals (**Table 4**).

In 129/Sv mice, the weight of the thymus and spleen after the administration of MPTP is significantly lower than in intact animals (**Table 4**). After hUC-MMSCs transplantation, the thymus weigh does not differ from the values of intact animals, and the spleen weight even exceeds those in the intact group of animals (**Table 4**).

Table 4. Behavioral indicators of experimental mice, M ± m.

Indicator	FVB/N mice			129/Sv mice		
	Intact (n = 9)	MPTP+ saline (control) (n = 6)	MPTP+ hUC-MMSCs (n = 7)	Intact (n = 9)	MPTP+ saline (control) (n = 6)	MPTP+ hUC-MMSCs (n = 10)
Thymus weight, mg	13.63 ± 0.8	11.66 ± 0.5*	15.0 ± 1.1&	15.8 ± 1.0	12.5 ± 0.9*	14.7 ± 0.8
Thymic index, mg/g, 10^{-3}	0.46 ± 0.03	0.37 ± 0.02*	0.55 ± 0.09	0.61 ± 0.09	0.37 ± 0.04*	0.55 ± 0.08&
Spleen weight, mg	137.7 ± 12.0	148.1 ± 9.0	112.0 ± 8.0	101.4 ± 7.9#	79.0 ± 6.8*#	200.6 ± 12.5*#&
Spleen index, mg/g, 10^{-3}	4.66 ± 0.5	4.86 ± 0.6	4.12 ± 0.5	3.99 ± 0.5	2.38 ± 0.3*#	6.67 ± 0.6*#&

*Note: * – p < 0.05 compared to the intact group; & – p < 0.05 compared to the control group (MPTP); # – p < 0.05 compared to FVB/N mice.*

Thus, in FVB/N and 129/Sv mice, the weight of the thymus is reduced regardless of their strain, while the spleen weight was reduced only in 129/Sv mice. The transplantation of hUC-MMSCs leads to the restoration of the thymus weight in mice of both strains and an increase in the spleen weight of 129/Sv mice.

The effect of hUC-MMSCs transplantation on the survival of mice with a model of parkinsonism. It was found that on the 7th, 14th, and 22nd days of the experiment, 8, 7, and 6 animals out of 12 were alive in the group of FVB/N mice that received MPTP, respectively, and 7 animals out of 10 survived in the group with hUC-MMSCs. After 7, 14, and 22 days of the experiment, 12, 10, and 6 animals out of 12 survived in the group of 129/Sv mice that received MPTP, respectively; in the group with hUC-MMSCs, all 10 animals out of 10 survived by the 22nd day. That is, on the 22nd day of the experiment, 50.0 % of mice in both control groups remained alive, while in the groups of FVB/N and 129/Sv mice with transplanted hUC-MMSCs the survival rate was 70.0 % and 100 %, respectively (**Fig. 2**).

Therefore, the transplantation of hUC-MMSC contributes to the survival of FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism. Differences in the death of mice in the early stages of the action of MPTP, which causes the development of oxidative stress, can be partially explained by the higher activity of some antioxidant enzymes in the brain of 129/Sv mice compared to FVB/N mice [29, 34].

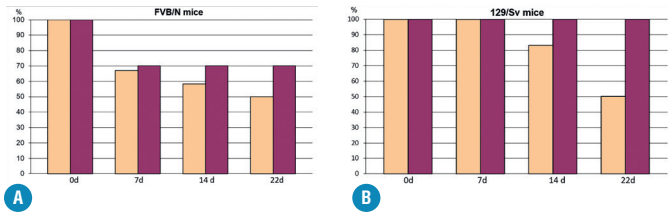

Fig. 2. The survival rate of FVB/N (A) and 129/Sv (B) mice assessed throughout the experiment, %. Data on groups 1 and 4 are not presented, as all animals remained alive at all observation times. Brown color – MPTP group, red color – MPTP+hUC-MMSCs group.

The comparative effects of MPTP in mice of different strains. It was observed that the administration of MPTP in FVB/N or 129/Sv mice leads to significant disturbances in motor, emotional, and exploratory activities, along with the appearance of signs of rigidity. The alterations in the functioning of the central nervous system in mice can be attributed to the damaging effect of MPTP on the structure of neurons in various parts of CNS, including the substantia nigra, cortex, thalamus, amygdala, and lumbar spinal cord [27, 34, 35].

It has been previously established by other authors and us that the effect of MPTP on mouse brain neurons can be mediated by factors of oxidative stress [3, 34] and pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ), which produce cells of activated microglia/macrophages and T-lymphocytes [2, 4, 36]. In our experiment, it was shown that the proportion of $CD3^+$ and $CD3^+CD11b^+$ cells, which according to the phenotype belong to T-lymphocytes and activated macrophages [37, 38], increases significantly in the brain of mice with the MPTP-induced model of parkinsonism. At the same time, an increase in the proportion of T-lymphocytes and activated macrophages was found in the brain of FVB/N mice and only activated macrophages – in 129/Sv mice. Our results are consistent with literature data on the effect of mouse genotype on the features of the formation of cells composition in CNS pathology that infiltrate the brain after CNS damage and mediate the development of neuroinflammation [39].

Attention is drawn to the decrease in the weight of the thymus in experimental FVB/N mice against the background of a simultaneous increase in the proportion of T-lymphocytes in the brain. It is known that the thymus is the source of various subpopulations of T-lymphocytes [40]. In the brain of patients with PD and in animals with the MPTP-induced model of parkinsonism, $CD4^+$ T-helpers were found to infiltrate this organ and participate in the development of neurodegeneration [4]. Therefore, it can be assumed that the increase in the proportion of T-lymphocytes in the brain of FVB/N mice with the MPTP-induced model of parkinsonism is associated with an increase in their migration from the periphery. In experimental 129/Sv mice, the content of T-lymphocytes in the brain remains unchanged, and under the influence of MPTP, the weight of not only the thymus, but also the spleen decreases. According to the literature, it is known about the damaging effect of MPTP on the lymphoid organs of mice [41].

Therefore, under the influence of MPTP, behavior, the content of T-lymphocytes and activated macrophages in the brain, as well as the weight of lymphoid organs change in FVB/N and 129/Sv mice. The effects of the neurotoxin are highly strain-dependent.

The efficacy of transplanted hUC-MMSCs in mice of different strains with MPTP-induced model of parkinsonism. Certain positive changes in the functional state of the central nervous system were revealed after the transplantation of hUC-MMSCs in FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism. The results obtained in 129/Sv mice are consistent with our previous data on the positive effect of a similar dose of hUC-MMSCs on the impaired behavior of mice with the cuprizone model of demyelination and neurodegeneration [42], as well as the effect of adipose-derived MMSCs in animals with the MPTP-induced model of parkinsonism [43]. In addition, other authors and we have shown a decrease in the number of neurons with structural changes and an increase in the number of intact neurons in the CNS (sensorimotor cortex, hippocampus) of animals with models of neurodegenerative pathology injected with hUC-MMSCs [44, 45]. Therefore, it is possible that the improvement of the behavior of FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism after hUC-MMSC transplantation may be associated with positive changes in the structure of CNS neurons. The study of the structure of brain neurons in such mice will be the subject of our further morphological analysis.

According to Zhang et al., hUC-MMSCs transplantation to animals with CNS pathology leads to an increased proliferation of neural progenitors, their secretion of growth and trophic factors, activation of neurogenesis and angiogenesis [46]. In addition, in the case of CNS pathology, transplanted MSCs, in particular hUC-MMSCs, show an antioxidant effect (reduction in the content of reactive radicals, increase in the expression of a number of antioxidant enzymes) [15, 47]. We have shown that under the influence of hUC-MMSCs in the brain of mice with a model of multiple sclerosis, the content of malondialdehyde decreases and the activity of antioxidant enzymes increases [42]. It is possible that transplanted hUC-MMSCs can act similarly in mice with MPTP-induced model of parkinsonism, since the content of malondialdehyde in their brains increases and the activity of antioxidant enzymes decreases [27, 34].

Another important mechanism of the protective effect of hUC-MMSCs in neurodegenerative pathology is their anti-inflammatory effect, which may be associated with the activation of IL-10 production, a decrease in IL-1β production and manifestations of active gliosis in the brain [30, 48, 49]. According to our data, under the influence of hUC-MMSCs in the brain of FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism, the content of neuroinflammatory cells (T-lymphocytes and activated macrophages) decreases to the values of intact animals, which coincides with an improvement in their functional state of the central nervous system. Taking into account the positive effect of cells on the impaired behavior of FVB/N and 129/Sv mice, we allow the possibility of a change in the phenotype of brain macrophages under these conditions from pro-inflammatory to anti-inflammatory, regenerative, in contrast to mice with the administration of MPTP only. Praet et al. showed the possibility of a similar change in the phenotype of macrophages in the brain of mice with toxin-induced models of CNS pathology [50].

It was found that after hUC-MMSCs transplantation, positive changes in the behavior of FVB/N and 129/Sv experimental mice had not only the same direction, but also some differences. Thus, under the influence of cells, in FVB/N mice, mainly motor activity improved and physical endurance increased, while in 129/Sv mice, emotional activity decreased and manifestations of rigidity decreased more clearly. According to the literature data, T-lymphocytes and macrophages of the brain, as well as the spectrum of factors produced by them, are important in the development of neurological deficits in animals with CNS pathology [39]. Therefore, it is possible that the differences in behavioral changes in FVB/N and 129/Sv experimental mice under the influence of hUC-MMSCs can be partially explained by the strain features of the composition of pro-inflammatory cells in the brain. Strain differences in the manifestations of oxidative stress in the brain of FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism may also be important [34].

Due to the above-mentioned mechanisms of the protective effect of hUC-MMSCs transplanted in animals with CNS pathology, there is an important question regarding the penetration of these cells into the brain. There are data that injected into the murine tail vein hUC-MMSCs can be found in the brain vessels of young animals with a model of LPS-induced neuroinflammation [48], and human hUC-MMSCs transplanted in this way into mice with CNS pathology are capable of differentiation in the neurogenic direction and synthesis of trophic factors [49]. Therefore, we do not exclude the possibility of penetration of transplanted hUC-MMSCs into the brain of mice with the MPTP-induced model of parkinsonism, with their subsequent implementation of biological activity. The paracrine effect of hUC-MMSCs may also be important in realizing their neuroprotective properties in neurodegenerative pathology of the CNS [51].

The immunomodulatory effect of MMSCs is well-documented in various pathological conditions [52]. We found that in FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism, the thymus weight increases after hUC-MMSCs transplantation. This cell effect may be related to the ability of MMSCs to suppress the activity of proapoptotic processes [53]. The positive effect of MMSCs was also observed in the spleen of 129/Sv mice, which can be partially implemented by the same anti-apoptotic mechanism.

In general, the results of experimental studies indicate the effectiveness of hUC-MMSCs transplantation already in the early stages of parkinsonism. At the same time, under the conditions of identical manifestations of CNS dysfunction in mice with a model of parkinsonism, the direction of changes in their behavior (motor or non-motor reactions) after the administration of hUC-MMSCs largely depended on the genotype of the animals. The genotype of the mice played a crucial role in shaping the appropriate composition of neuroinflammatory cells (T-lymphocytes, activated macrophages) in the brain, both under the influence of neurotoxins and in the manifestation of a positive effect from transplanted hUC-MMSCs. In the future, the results can be the basis for the development of personalized cell therapy for parkinsonism using hUC-MMSCs according to the individual's genetic characteristics.

CONCLUSION

1. ***In adult mice of the FVB/N and 129/Sv strains, exposure to the neurotoxin MPTP induces motor and non-motor behavior disorders, an increase in the content of T-lymphocytes and activated macrophages in the brain, and a decrease in the weight of the thymus and spleen. The observed changes in the studied indicators are largely dependent on the genotype of the animals.***
2. ***The transplantation of hUC-MMSCs demonstrates a positive impact on the functional state of the central nervous system in FVB/N and 129/Sv mice with the MPTP-induced model of parkinsonism. The beneficial effects of hUC-MMSCs on the behavior of experimental mice exhibit some strain differences and are observed concomitant with the restoration of the content of T-lymphocytes and activated macrophages in the brain.***
3. ***The transplantation of hUC-MMSCs demonstrates an immunomodulatory effect on the weight of lymphoid organs in mice of both strains with the MPTP-induced model of parkinsonism.***
4. ***The administration of hUC-MMSCs promotes the survival of both FVB/N and 129/Sv mice compared to animals treated solely with MPTP.***

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Ефекти трансплантації мультипотентних мезенхімальних стромальних клітин пуповини людини мишам різних ліній із експериментальною моделлю паркінсонізму

Лабунець І. Ф.[1,2], Пантелеймонова Т. М.[1,2], Кирик В. М.[1,2], Топорова О. К.[3], Пікус П. О.[1,3], Літошенко З. Л.[1,2]

[1]*Інститут генетичної та регенеративної медицини ДУ "Національний науковий центр "Інститут кардіології, клінічної та регенеративної медицини ім. акад. М. Д. Стражеска Національної академії медичних наук України", Київ, Україна*
[2]*ДУ "Інститут геронтології ім. Д. Ф. Чеботарьова Національної академії медичних наук України", Київ, Україна*
[3]*Інститут молекулярної біології та генетики Національної академії наук України, Київ, Україна*

РЕЗЮМЕ

Одним із перспективних напрямків клітинної терапії хвороби Паркінсона/паркінсонізму є трансплантація мультипотентних мезенхімальних стромальних клітин (ММСК) пуповини людини, ефективність якої може залежати від генотипу реципієнта.

***МЕТА ДОСЛІДЖЕННЯ** — порівняти вплив трансплантованих ММСК пуповини людини на поведінку, вміст Т-лімфоцитів і макрофагів в головному мозку і лімфоїдних органах мишей різних ліній із моделлю паркінсонізму.*

***МЕТОДИ.** Дорослим (6-7 міс.) самцям мишей лінії FVB/N (гаплотип H-2^q) і 129/Sv (гаплотип H-2^b) одноразово вводили нейротоксин 1-метил-4-феніл-1,2,3,6-тетрагідропіридин (МФТП) у дозі 30 мг/кг (контрольна група), а через 7 діб у хвостову вену – ММСК пуповини людини у дозі 500 тис. клітин. Оцінювали показники поведінки в тестах "відкрите поле", на ригідність і ротарод тесті; вимірювали відносний вміст Т-лімфоцитів і активованих макрофагів в головному мозку, а також масу лімфоїдних органів.*

***РЕЗУЛЬТАТИ.** Під впливом МФТП у мишей лінії FVB/N і 129/Sv зменшувалась кількість стійок, «зазирань у нірки», довжина тіла і кроку, зростала кількість болюсів, а у мишей лінії 129/Sv також знижувалась кількість перетнутих квадратів у тесті "відкрите поле". У головному мозку мишей обох ліній зростав вміст активованих макрофагів і, крім того, кількість Т-лімфоцитів у мишей лінії FVB/N. Маса тимуса зменшувалась у мишей обох ліній, тоді як маса селезінки – лише у мишей лінії 129/Sv. Під впливом ММСК у мишей лінії FVB/N поліпшувалась переважно рухова активність, тоді як у мишей лінії 129/Sv – емоційна активність, прояви ригідності зменшувались у мишей обох ліній; вміст Т-лімфоцитів і активованих макрофагів у головному мозку мишей обох ліній, як і маса тимуса відповідали значенням інтактних тварин. Трансплантація ММСК сприяла виживанню мишей лінії FVB/N і 129/Sv із МФТП-моделлю паркінсонізму.*

***ВИСНОВОК.** Прояви порушень поведінки, зміни вмісту Т-лімфоцитів, активованих макрофагів в головному мозку і маси лімфоїдних органів у мишей із МФТП-моделлю паркінсонізму, а також позитивні ефекти трансплантованих ММСК пуповини людини у таких тварин в значній мірі залежать від їх генотипу за системою H-2 (аналог HLA людини). Результати можуть бути підгрунтям для розробки персоніфікованої клітинної терапії цієї патології з використанням ММСК пуповини.*

***КЛЮЧОВІ СЛОВА:** мультипотентні мезенхімальні стромальні клітини пуповини людини; паркінсонізм; поведінкові реакції; Т-лімфоцити і макрофаги головного мозку; тимус; селезінка*