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THE EFFECT OF STEM CELLS ON THE FUNCTIONAL STATE OF LIVER TISSUE AGAINST THE BACKGROUND OF A LIVER CIRRHOSIS MODEL (EXPERIMENTAL STUDY)

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◆ ***Relevance.*** Treatment of liver cirrhosis is an extremely important problem of modern medicine. Improvement of liver function in this category of patients is important not only for hepatology, but also for surgery, since surgical interventions on the liver in this pathology are often accompanied by the development of liver failure.

Purpose. To evaluate the effect of cell therapy on liver function in the experiment.

Materials and methods. The article presents the results of the experimental use of use of stem cells in simulated liver cirrhosis. The experiment was performed on 132 female c57black mice, which were between 12 and 18 weeks old. After forming a model of liver cirrhosis, in order to assess the effect of cell therapy on the function of liver tissue, individuals were injected with stem cells through the vessels of the peripheral bed and intraportally. 30 days after cell therapy, the blood levels of ALT, AST, alkaline phosphatase, plasma diene conjugants, plasma malondialdehyde, plasma superoxide dismutase, and glutathione peroxidase were evaluated.

Conclusion. According to the findings, obtained in the experiment, the use of cell therapy against the background of simulated cirrhosis of the liver contributed to a decrease in the severity of cytolytic and cholestatic syndromes, stimulation of liver protein function, suppression of free radical oxidation and stimulation of the antioxidant system. At the same time, the best effect was achieved when the cell structures were introduced not into the peripheral vessels, but directly into the vascular bed of the liver.

◆ **Keywords:** liver cirrhosis; cell therapy; experimental improvement of liver function; effect of stem cells on liver function.

ВЛИЯНИЕ СТВОЛОВЫХ КЛЕТОК НА ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ПЕЧЕНОЧНОЙ ТКАНИ НА ФОНЕ МОДЕЛИ ЦИРРОЗА ПЕЧЕНИ (ЭКСПЕРИМЕНТАЛЬНОЕ ИССЛЕДОВАНИЕ)

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◆ ***Актуальность.*** Лечение цирроза печени является крайне важной проблемой современной медицины. Улучшение функции печени у данной категории больных имеет значение не только для гепатологии, но и для хирургии, поскольку оперативные вмешательства на печени при подобной патологии зачастую сопровождаются развитием печеночной недостаточности.

Цель — оценить влияние клеточной терапии на функцию печени в эксперименте.

Материалы и методы. В статье представлены результаты экспериментального исследования использования стволовых клеток при смоделированном циррозе печени. Эксперимент был проведен на 132 мышах-самках линии C57black. Возраст животных — от 12 до 18 нед. После формирования модели цирроза печени с целью оценки влияния клеточной терапии на функцию печеночной ткани особям через сосуды периферического русла и внутрипортально были введены стволовые клетки. Через 30 сут после клеточной терапии у особей оценивали активность аланинаминотрансферазы, аспартатаминотрансферазы, щелочной фосфатазы, супероксиддисмутазы плазмы и глутатионпероксидазы в крови, уровень диеновых конъюгатов плазмы, малонового диальдегида плазмы.

Заключение. Было установлено, что клеточная терапия на фоне смоделированного цирроза печени способствовала уменьшению выраженности цитолитического и холестатического синдромов, стимуляции белковой функции печени, подавлению процессов свободнорадикального окисления и стимуляции антиоксидантной системы. При этом наилучший эффект был достигнут, когда клеточные структуры вводили не в периферические сосуды, а непосредственно в сосудистое русло печени.

◆ **Ключевые слова:** цирроз печени; клеточная терапия; улучшение функции печени в эксперименте; влияние стволовых клеток на функцию печени.

Introduction

Liver cirrhosis is becoming an increasingly common pathology that occurs at the final stage of chronic liver diseases [1–3]. Because of the lack of drugs that can cease the development of liver tissue fibrosis and significantly improve liver function, the search for alternative treatment methods is imperative; one of which is cell therapy. Since this treatment method is still under study, preliminary experimental studies are required to assess its efficiency [4]. Currently, there is no consensus on the mechanisms of the effect of stem cells on the damaged organ. It is assumed that both transdifferentiation of the injected cells [5] and their fusion with normal cells of the organ [6] are possible, as well as the implementation of the two mechanisms described earlier [7]. In our study, in addition to assessing the effect of stem cells on the function of hepatic tissue, we compared the methods of delivery of cell structures to the recipient's body. The researchers proposed various methods of cell delivery, including intravenous and intrahepatic administration and administration into the vascular bed of the liver and spleen [8–10]. The administration of stem cells into the peripheral vascular bed is an easier way, but in this case, the cells survive not only in the damaged organ but also in other organs and tissues [11]. In our experimental study, we analyzed the effect of stem cells on liver function in the case of a liver cirrhosis model, comparing intraportal and intravenous administration of stem cells.

The study aimed to assess the effect of cell therapy on the functional state of the liver tissue in the case of a liver cirrhosis model.

Materials and methods

The experimental study was conducted on 132 C57 black female mice. The animals were 12 to 18 weeks of age. The rules of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes were observed during the experimental study. The animals were kept in the vivarium of the university and had free access to food and water. Surgical interventions on animals were performed using general anesthesia. The animals were also sacrificed under general anesthesia by decapitation. Before the experiment, 30 individuals were sacrificed (group 5) to determine the normal indicators of free radical oxidation and antioxidant system and isolate stem cells by obtaining an aspirate from the femoral and tibial bones of the animals. To obtain stem cells, the diaphysis of the femoral and tibial bones was washed with a solution containing 100 U/mL of penicillin, 12 mM L-glutamine, 15% fetal bovine serum, and 100 μg/mL of streptomycin. The isolated cells were then placed in tubes containing the growth medium (5 mL) and centrifuged for 10 min. After completing the centrifugation process, the resulting precipitate was resuspended in growth medium to $1 \cdot 10^6$ cells/mL. The cell structures obtained were inoculated into 25 cm^2 culture flasks, followed by cultivation in an incubator (T = 37°C, 5% CO_2). The cultivation was completed upon achieving confluence. In total, three cell passages were performed; the cell phenotype was confirmed by flow cytometry.

The remaining 102 individuals were divided into three groups (34 individuals each), with the

subsequent formation of a liver cirrhosis model in each group. Liver cirrhosis was modeled using 50% sovtol diluted in olive oil (0.25 mL solution per 100 g of animal body weight) and replacing drinking water with 10% C_2H_5OH (V.A. Myshkin, RF patent 2197018) [12]. Thirty days after the beginning of the model formation, four individuals were randomly selected from each group, which formed group 4 ($n = 12$). Group 4 was withdrawn from the experiment to confirm the presence of liver cirrhosis. Group 1 received cell therapy with intravenous injection of cell structures, group 2 received cell therapy with intraportal injection of stem cells, and group 3 did not receive any therapy since they were used to assess the possible spontaneous regression of the model formed and confirm the integrity of the experiment.

To assess the effect of cell therapy on the functional state of the liver tissue before the start of the experiment in the presence of the liver cirrhosis model and 30 days after the therapy, the level or activity of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, plasma diene conjugates, plasma malondialdehyde, plasma superoxide dismutase, and blood glutathione peroxidase was determined in the three groups. Statistical data processing was conducted using the Statistica 10.0 and Microsoft Excel 2010 software package with the use of the methods of variation statistics, calculating the mean values (M), assessing the probability of discrepancies (m), and assessing the significance of changes using Student's test. The difference in mean values was considered significant at $p < 0,05$.

Research results

Before the start of the formation of the liver cirrhosis model, the aforementioned blood parameters were determined in all individuals. All indicators were within the normal ranges, and there were no significant differences between the groups ($p > 0.05$). Blood biochemical parameters were assessed in individuals of all three groups 30 days after the formation of a liver cirrhosis model and then 30 days after liver cirrhosis therapy. Table 1 presents the dynamics of ALT activity during the experiment.

Table 1 shows that in the formed liver cirrhosis model in all three groups, there was an increase in ALT activity without significant differences between the groups ($p > 0.05$). A decrease in ALT activity was detected 30 days after therapy in groups 1 and 2. At the same time, in the group with intraportal administration of stem cells (group 2), the decrease was more pronounced than in the group with intravenous administration of cell structures. In group 3, there was no tendency

Table 1 / Таблица 1

Dynamics of alanine aminotransferase (ALT) indicators (U/L) in groups 1, 2, and 3 before the experiment, against the background of liver cirrhosis, and 30 days after the therapy

Динамика показателей аланинаминотрансферазы (ЕД/л) в первой – третьей группах до эксперимента, на фоне формирования цирроза печени и через 30 сут после терапии

Group	Timing of determination of ALT activity	Value	Standard deviation	Minimum	Maximum	Median	Lower quartile	Upper quartile
1	Before the experiment	49.0	1.7	45.7	53.7	48.9	47.9	50.3
	30 days after liver cirrhosis formation	144.8	2.3	139.8	149.7	144.8	143.3	146.6
	30 days after the therapy	110.0	1.3	107.3	113.2	110.1	109.3	110.8
2	Before the experiment	50.0	1.2	47.3	52.9	50.1	49.5	50.9
	30 days after liver cirrhosis formation	144.9	2.1	140.3	149.6	144.6	143.7	146.3
	30 days after the therapy	74.8	1.3	71.2	77.4	74.8	74.3	75.5
3	Before experiment	49.0	1.4	45.8	51.7	49.1	48.5	49.6
	30 days after liver cirrhosis formation	145.1	1.8	140.9	148.9	144.8	144.0	145.9
	30 days after the therapy	148.3	1.5	145.6	152.2	148.3	147.3	149.0

Table 2 / Таблица 2

Dynamics of aspartate aminotransferase (AST) indicators (U/L) in groups 1, 2, and 3 before the experiment, against the background of liver cirrhosis, and 30 days after the therapy

Динамика показателей аспартатаминотрансферазы (ЕД/л) в первой – третьей группах до эксперимента, на фоне формирования цирроза печени и через 30 сут после терапии

Group	Timing of determination of AST activity	Value	Standard deviation	Minimum	Maximum	Median	Lower quartile	Upper quartile
1	Before the experiment	78.2	2.4	70.6	81.4	78.5	77.0	80.2
	30 days after liver cirrhosis formation	270.2	2.4	263.8	276.5	269.6	268.9	271.3
	30 days after the therapy	251.3	1.6	247.7	254.2	251.4	250.4	252.4
2	Before the experiment	78.2	2.2	72.9	82.3	78.6	76.4	79.4
	30 days after liver cirrhosis formation	270.0	3.1	264.1	274.6	270.2	268.2	273.0
	30 days after the therapy	200.3	2.2	196.1	205.5	200.1	198.9	201.7
3	Before the experiment	77.9	1.9	74.2	81.7	78.0	76.8	78.8
	30 days after liver cirrhosis formation	270.3	2.4	265.0	274.7	270.5	269.2	272.1
	30 days after the therapy	273.8	1.5	270.9	276.9	273.6	272.8	274.8

toward a decrease in the indicator, which confirmed the absence of spontaneous regression of the model. All differences between the groups were confirmed statistically ($p < 0.05$).

Table 2 presents the dynamics of AST activity during the experiment.

In presence of the liver cirrhosis model, the indices of AST and ALT were increased in all groups without significant differences between the groups ($p > 0.05$). Thirty days after therapy, the greatest decrease in indicators was recorded in the group with intraportal injection of cell structures. In the group with intravenous administration of stem cells, AST activity was also decreased, but to a lesser extent than in group 2. In group 3, the mean values of AST activity increased mildly compared with the indicators that were obtained in the case of the liver cirrhosis model, which confirmed the absence of spontaneous regression of changes in the presence of the model.

Table 3 presents the changes in the activity of alkaline phosphatase in the experimental study.

In the liver cirrhosis model of all groups, the activity of alkaline phosphatase increased without statistically significant differences between the groups ($p > 0.05$). Thirty days after the cell therapy in groups 1 and 2, a decrease in the alkaline phosphatase values was registered, whereas in the group with intraportal administration, the decrease in indicators was more pronounced. In group 3, there was no tendency to decrease, which confirmed the absence of spontaneous regression of the formed liver cirrhosis model.

Table 4 shows the dynamics of the albumin level in the study groups during the experiment.

Table 4 shows that in presence of the liver cirrhosis model, the mean albumin values decreased in all three groups ($p > 0.05$), which confirmed the model formation. Thirty days after the therapy, the albumin levels increased by 10.5% and 36.8% in groups 1 and 2, respectively. In group 3, the indicators remained without significant dynamics. Significant differences were revealed between all three groups ($p < 0.05$). The data presented demonstrate the effect of cell therapy on the stimulation of liver protein function, and intraportal administration of stem cells was more effective than intravenous administration.

In addition to analyzing the activity of ALT, AST, ALP, and albumin level, the indicators of free radical oxidation and the antioxidant system were determined, including the concentration of plasma diene conjugates and plasma malondialdehyde

Table 3 / Таблица 3

Dynamics of indicators of alkaline phosphatase (U/L) in groups 1, 2, and 3 before the experiment, against the background of liver cirrhosis, and 30 days after the therapy

Динамика показателей щелочной фосфатазы (ЕД/л) в первой – третьей группах до эксперимента, на фоне формирования цирроза печени и через 30 сут после терапии

Group	Timing of determination of alkaline phosphatase activity	Value	Standard deviation	Minimum	Maximum	Median	Lower quartile	Upper quartile
1	Before the experiment	87.5	1.8	84.1	90.7	87.7	85.9	88.7
	30 days after liver cirrhosis formation	229.8	2.1	226.1	234.4	229.4	228.3	231.2
	30 days after the therapy	221.0	2.5	216.8	228.0	221.1	219.6	222.5
2	Before the experiment	86.9	1.7	83.0	89.5	87.3	85.8	88.3
	30 days after liver cirrhosis formation	230.0	2.2	225.8	235.1	230.4	228.4	231.3
	30 days after the therapy	197.0	2.4	191.6	201.9	197.5	195.2	198.9
3	Before the experiment	86.7	2.1	82.6	91.5	86.4	85.7	87.9
	30 days after liver cirrhosis formation	230.4	1.7	227.7	234.5	230.4	228.8	231.8
	30 days after the therapy	240.9	1.9	237.2	245.0	241.3	239.2	242.0

Table 4 / Таблица 4

Dynamics of albumin indicators (g/L) in groups 1, 2, and 3 before the experiment, against the background of liver cirrhosis, and 30 days after the therapy

Динамика показателей альбумина (г/л) в первой – третьей группах до эксперимента, на фоне формирования цирроза печени и через 30 сут после терапии

Group	Timing of determination of albumin level	Value	Standard deviation	Minimum	Maximum	Median	Lower quartile	Upper quartile
1	Before the experiment	3.9	0.9	2.2	5.5	3.8	3.1	4.9
	30 days after liver cirrhosis formation	1.9	0.1	1.7	2.1	1.9	1.8	1.9
	30 days after the therapy	2.1	0.0	2.1	2.2	2.1	2.1	2.1
2	Before the experiment	3.9	0.8	2.5	5.5	3.9	3.4	4.4
	30 days after liver cirrhosis formation	1.9	0.1	1.7	2.1	1.9	1.9	2.0
	30 days after the therapy	2.6	0.0	2.5	2.6	2.6	2.6	2.6
3	Before the experiment	3.7	0.7	2.2	5.0	3.7	3.1	4.2
	30 days after liver cirrhosis formation	1.9	0.1	1.7	2.1	1.9	1.8	2.0
	30 days after the therapy	1.8	0.0	1.8	1.8	1.8	1.8	1.8

and the activity of plasma superoxide dismutase and blood glutathione peroxidase.

Table 5 presents the changes in these indicators.

Table 5 shows that in the presence of the liver cirrhosis model, the levels of diene conjugates and malondialdehyde increased by 1.4 and 2.1 times, respectively, and the activity of superoxide dismutase and glutathione peroxidase decreased on average by about two times, which confirmed the formation of the model. Although 30 days after cell therapy, the indices of free radical oxidation decreased, and the indices of the antioxidant

Table 5 / Таблица 5

Динамика показателей перекисного окисления и антиоксидантной системы в группах исследования
Dynamics of peroxidation and antioxidant system indicators in the study groups

Group	Diene conjugates in blood plasma, mmol/L	Malondialdehyde in blood plasma, mmol/L	Superoxide dismutase in blood plasma, mmol/min · L	Glutathione peroxidase in blood, U/g Hb
Group 5 (normal values)	0.60 ± 0.02	0.07 ± 0.02	1111.57 ± 119.6	362.97 ± 18.3
Group 4 (liver cirrhosis model)	0.85 ± 0.04	0.15 ± 0.04	639.20 ± 75.5	174.01 ± 9.1
Group 1 (30 days after the therapy)	0.70 ± 0.18	0.09 ± 0.03	675.95 ± 134.5	189.21 ± 35.1
Group 2 (30 days after the therapy)	0.63 ± 0.12	0.08 ± 0.02	789.20 ± 186.7	242.47 ± 11.9
Group 3 (30 days after the therapy)	0.83 ± 0.02	0.18 ± 0.02	641.20 ± 119.6	172.01 ± 18.3

system increased in groups 1 and 2, and more significant dynamics were revealed in the group with intraportal administration of cell structures. In group 3, the indices of free radical oxidation and antioxidant system remained without significant dynamics, which supported the stability of the formed liver cirrhosis model. Significant differences between the groups were confirmed statistically ($p < 0.05$).

Discussion

The liver is a unique organ that has a great aptitude for regeneration [13]. However, this aptitude decreases sharply with prolonged exposure to a damaging agent. To date, there are no drugs that can adequately help patients with diffuse liver diseases, and often, orthotopic liver transplantation is the only chance to prolong life. However, difficulties with the availability of donor organs, the high cost of both the surgical intervention itself, and the postoperative management of this category of patients significantly reduce the availability of this type of treatment [14, 15]. Recently, most researchers have paid special attention to regenerative therapy, in which the efficiency is primarily evaluated in experiments.

As a result of our study, during cell therapy, the protein function of the liver improved, which was associated with the possible transdifferentiation of cell structures administered into hepatocytes by many researchers [16–18]. In addition, the use of cell technologies contributed to a decrease in the activity of liver enzymes. Most authors confirm a similar effect when using cell therapy [18, 19]. However, there is a significant difference between the rate and degree of decrease in liver enzyme activity, which is probably associated with the use of different models of the formation of diffuse liver diseases [18, 20, 21]. In addition to analyzing the changes in blood biochemical parameters, the indicator levels of free radical and antioxidant systems were assessed, since they are significant markers of toxic damage to the liver tissue. During the cell therapy, a decrease in the indices of free radical oxidation and an increase in the activity of superoxide dismutase and glutathione peroxidase were noted, which is extremely important, since the accumulation of lipid peroxidation products causes even greater damage to liver cells, thereby aggravating the course of the disease [22, 23].

In a comparative analysis of intravenous and intraportal administration of stem cells, it was found that a positive effect was achieved in both cases. However, with the intraportal administration, the improvement was more significant, which could be because cell structures can be partially fixed in various organs and tissues with intravenous administration [24].

Conclusion

During our experimental study, it was revealed that cell therapy in the case of a liver cirrhosis model contributed to a decrease in the severity of cytolytic and cholestatic syndromes, stimulation of the protein function of the liver, suppression

of free radical oxidation, and stimulation of the antioxidant system. Here, the best effect was achieved when the cell structures were administered not into the peripheral vessels but directly into the vascular bed of the liver.

Conflict of interest. The authors declare no conflict of interest.

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