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ACTIVATION OF REGENERATIVE PROCESSES IN THE LIVER WHEN USING CELL-BONE MARROW TOTAL RNA

N.A. Onishchenko[1], E.V. Fomenko[1], A.O. Nikolskaya[1], Z.Z. Gonikova[1], M.Yu. Shagidulin[1, 2], M.V. Balyasin[2], A.V. Elchaninov[3], V.I. Sevastyanov[1]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

[3] Research Institute of Human Morphology, Moscow, Russian Federation

Objective: to study the cellular mechanisms of activation of regenerative processes in the liver when using total RNA (tRNA) of bone marrow cells (BMCs) based on an extended liver resection (ELR) model. **Materials and methods.** Male Wistar rats (n = 80) with ELR model (70%) were divided into 2 groups: group 1 (control group) had a single saline injection, while group 2 (experimental group) received a single tRNA injection at a 30 μg/100 g dose of animal weight. The biochemical parameters of liver function and weight were monitored over time. Also monitored were microstructural changes in hepatocytes 48 hours after ELR by examining mitotic activity, caspase-9 expression and morphometric parameters. **Results.** It was found that in group 2, in comparison to group 1, there was faster normalization of biochemical parameters (by 10–14 days), a higher mitotic index of hepatocytes (23.45‰ versus 5.37‰), and initially sharper decrease and then faster recovery of liver mass (by 10–12 days versus 18–20 days). Both groups showed almost total expression of caspase-9, including in mitotically splitting hepatocytes. Group 1 demonstrated decreased values of morphometric parameters of single and binuclear cells, decreased number of binucleated hepatocytes and increased total density of hepatocytes as compared to the intact liver. Intraperitoneal administration of tRNA increased morphometric parameters of mononuclear hepatocytes, did not affect their number, but increased the area of the nuclei of binuclear hepatocytes as compared to the control group. **Conclusion.** The proven capability of cell-bone marrow total RNA to simultaneously support apoptosis in liver cells after ELR and induce mitotic activity indicates that tRNA can switch activated apoptosis to cell proliferation at the early phase of the regenerative process. This effect may be due to the presence of regulatory RNA molecules in tRNA, including numerous non-coding RNAs.

Keywords: bone marrow cells, total RNA, liver, experimental model, resection, regeneration.

INTRODUCTION

From recent publications, total RNA (tRNA) isolated from bone marrow cells (BMC) is known to have an inductive effect on the processes of regenerative regeneration of organs [1], however, the mechanisms of triggering its regulatory effect at the cellular level remain unclear. Meanwhile, the choice of a strategy and the improvement of the tactics of using cellular products cannot be carried out without considering the mechanisms involved in the regeneration process.

According to established views, organ regeneration occurs within the activation of an evolutionarily developed nonspecific adaptive syndrome (NAS) of cellular systems, which already at the early stages of development stimulates a complex of stereotypical adaptive changes in cells aimed at survival by mobilizing their own preserved reserves and the subsequent formation of stable adaptation by including regenerative mechanisms [2, 3]. When modeling 70% of hepatectomy, which has become a classical model for studying regeneration processes in the liver, it was shown that the ability of the cellular system to ensure the self-correction is largely dependent on the degree of activation in the cells of the remaining parts of the liver of the earliest manifestations of the adaptation syndrome, such as autophagy and apoptosis. The ability of the cellular system to ensure the correction of its existence, to be sensitive to various correcting factors, and to launch an effective regenerative process largely depends on this [4–7].

The **purpose** of the present work is to study the dynamics of the formation of recovery processes in the damaged liver after a single intraperitoneal injection of BMC tRNA on an experimental model of extensive resection of rat liver, monitoring quantitative changes in specific indicators of liver function and nonspecific substance (microstructural) changes in cells, which are characteristics of development phases in them NAS.

Corresponding author: Zalina Gonikova. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (966) 188-33-33. E-mail: zalina3393@gmail.com

MATERIALS AND METHODS

All studies using laboratory animals were performed in compliance with the bioethical principles approved by the European Convention for the Protection of Vertebrate Animals (2005).

The study was performed on 130 male Wistar rats weighing 250–300 g, in 80 of which the ORP model was reproduced [8], the rest of the rats were used to obtain unsorted mononuclear BMCs and to isolate tRNA from them. Before modeling RRP, the operated rats were anesthetized by inhalation with diethyl ether, then, following the rules of asepsis and antiseptics, the abdominal cavity was opened, the liver was removed into the wound, and ligatures were sequentially applied to the bases of the median, left lateral, and right upper lobes of the liver, after which they were removed (70–75% of the total liver mass). The operation was always performed in the morning (from 10 am to 12 noon), when the daily rhythm of mitotic activity of liver cells is minimal. In the early postoperative period, the operated animals always developed a clinical picture of acute liver failure.

After ELR, all animals were divided into two groups; group 1 – control (n = 40), in which rats were once intraperitoneally injected with 1.0–1.5 ml of saline; group 2 – experimental (n = 40), in which, 3–5 hours after ORP, total RNA (tRNA) isolated from the unsorted mononuclear BMC fraction of healthy donor rats was injected once intraperitoneally at a dose of 30 μg/100 g of body weight, dissolved in 1.0–1.5 ml of saline.

Total RNA from the BMC mononuclear fraction was isolated with the ExtractRNA reagent (Evrogen (Russia) according to the manufacturer's instructions, which made it possible to obtain about 148.5 ± 22.3 μg RNA from each 30–35 × 10^6 cells.

The dynamics of spontaneous restoration of hepatic homeostasis in the body after ELR and the effect of tRNA on this process were studied by measuring the content of total protein and total bilirubin in blood serum in the early postoperative period (within 14 days), as well as the activity of hepatic cytolysis enzymes: alanine aminotransferase (ALT), aspartic aminotransferase (ASAT) and alkaline phosphatase (ALP) – by standard methods on a biochemical analyzer "Arik-test", Germany. We also investigated the rate of overcoming the critical mass of the liver remnant and its restoration to its initial values after ELR within 28 days. For this, in each operated animal, immediately after ELR, the resected part of the liver was weighed, which was taken as 70% of the total liver weight, and then, based on these measurements, the initial liver weight was calculated for each animal. Then, at each study period, the remaining liver was explanted, its weight was determined by weighing, and the obtained values were compared with the calculated initial liver weight for this animal.

The nature of the induction effect on the recovery processes in the liver of critical injury during the creation of the ELR model (group 1) and the results of the use of tRNA against the background of ELR (group 2) were judged by quantitative assessment of changes in the parameters of the microstructural state of liver cells. For this, first of all, the mitotic activity of hepatocytes in the liver remnant was investigated at 24, 36, 48 and 72 hours, as well as on the 5th, 7th and 10th days after ELR in groups 1 and 2. At the indicated time, the liver was excised and histological drugs; we stained tissue sections with hematoxylin and eosin and determined in 30 fields of view the number of mitotically dividing hepatocytes in ppm (‰) and calculated the mitotic index (MI).

The morphometric assessment of the state of hepatocytes was also carried out on liver sections stained with hematoxylin and eosin. Using a Nikon Eclipse 50i microscope equipped with a digital camera (Japan), micrographs of liver sections were obtained at ×400, on which, using the ImageJ software package, the areas of hepatocytes and their nuclei were measured with subsequent calculation of the cytoplasm and binucleated hepatocytes with the subsequent calculation of their percentage and the number of cells per unit section area.

Since ELR is known to be a critical trauma and the early stage of the regeneration process is always accompanied by the appearance of signs of cellular autophagy [4, 5] and reversible cell death – reversible apoptosis [6], 3 μm thick liver sections were stained with rabbit antibodies to the protein of the proteolytic cell system – Caspase 9 (Abcam) at a dilution of 1:100 in PBS with the addition of 0.1% Tween 20 and 5% BSA for immunohistochemical detection of signs of reversible apoptosis of hepatocytes in the early phase of the regeneration process after 48 hours. Samples were washed and secondary antibodies against rabbit IgG conjugated to HRP (Agilent Dako) in PBS-T solution with 5% BSA were applied. Then there was a staining with DAB (Abcam); the nuclei were stained with Mayer's hematoxylin (BioVitrum). Microscopy of the samples was made with Nikon Eclipse TE2000 optical microscope.

Statistical processing of the results was performed in R software environment, the character of the distribution of features was determined by Shapiro – Wilk test. The significance of the differences in the studied parameters in the two compared groups was assessed using the Wilcoxon and Student t-tests, considering the Holm-Bonferonni correction.

RESULTS AND DISCUSSION

Of the 80 rats in which ELR was modeled with the development of acute liver failure, 6 animals died within the first 5 days after liver resection, and the overall mortality was 7.5%. All animals that died after ELR belonged to control group 1 (no special therapy, n = 40), and within this group the mortality rate was 15%. In experimental

group 2 (n = 40), there was no lethality during the entire observation period.

The absence of lethality in experimental group 2 was accompanied by an accelerated rate of restoration of hepatic homeostasis in the body, which was expressed in an earlier normalization of biochemical parameters of liver function: the level of total protein, total bilirubin and the activity of cytolytic enzymes in the blood serum.

Tables 1 and 2 show the results of a dynamic study of the activities of AST, ALT, ALP, the level of total bilirubin and total protein in the blood serum of rats after modeling ELR in the control group (Table 1) and the experimental group with the introduction of tRNA (Table 2). In the control group, the cytolysis indices in the surviving animals were sharply increased during the first 5 days after ELR, then they stabilized, and only starting from the 7–10th day there was a clear tendency towards their normalization. The indices of total protein within 2 and 3 days were sharply reduced compared to the initial level and starting from 5–7 days the level of protein in the blood serum gradually increased but did not reach the initial values of the norm until the end of observations (14 day). In the experimental group, where tRNA was injected after ELR (Table 2), the cytolysis indices after ELR remained stably high only for 1–3 days, but by the 5th day there was a clear decrease in the activity of all studied liver enzymes in the rat blood serum. compared with control ($p < 0.05$) at the same time. As a result, in the experimental group with the introduction of tRNA, the values of the studied parameters in the blood serum approached the norm already on the 10th day and did not differ from the initial values by the 14th day of observation, while in the control group, the normalization of all the studied parameters did not occur even by the 14th day. -th day. A higher rate of recovery of hepatic homeostasis indices in the body was accompanied in the experimental group by a significant increase in the activity of proliferative processes in the resected liver after ELR compared with the control.

The study of the mitotic activity of hepatocytes in the resected liver made it possible to establish its sharp activation 48 hours after modeling the ELR in both groups 1 and 2 compared with the baseline level: the initial level of mitotic activity, assessed before liver resection by the mitotic index (MI) was 0.2–0.3‰ (1–2 mitosis per 30 fields of view). However, 48 hours after ELR, the severity of MI activation in the study groups became different: in the 1st, control group, MI was 5.378‰ (there were 36 mitoses per 6693 cells), while in the 2nd, experimental group, MI was 23.45‰ (227 mitoses were

Table 1

Dynamics of changes in the levels of total protein, total bilirubin, and the activity of cytolysis enzymes (AlAT, AsAT, and ALP) in blood serum after ELR and infusion of physiological saline (PS) (control group, n = 40)

Observation time (days)	Group 1 (control, saline), n = 40				
	AsAT, U/L	AlAT, U/L	AP, U/L	Total bilirubin, μM/L	Total protein, g/l
Initial values	58 ± 8.0	40 ± 6.0	240 ± 24	2.2 ± 0.7	98 ± 20
2	570 ± 29*	310 ± 10*	1102 ± 21*	10.2 ± 2.0*	21 ± 16*
3	490 ± 20*	320 ± 21*	1009 ± 29*	12.3 ± 1.5*	24 ± 11*
5	420 ± 27*	290 ± 18*	982 ± 22*	10.8 ± 1.3*	36 ± 13*
7	360 ± 24*	282 ± 15*	893 ± 24*	9.0 ± 1.9*	41 ± 9.0*
10	199 ± 22*	169 ± 18*	560 ± 24*	7.3 ± 2.0*	55 ± 6.0*
14	100 ± 14*	121 ± 13*	340 ± 20*	3.5 ± 1.0	61 ± 7.0

Note. * – $p < 0.05$ compared to baseline.

Table 2

Dynamics of changes in the content of total protein, total bilirubin and the activity of cytolysis enzymes (AlAT, AsAT, and ALP) in the blood serum after ELR and infusion of tRNA at a dose of 30 μg/100 g of animal weight (n = 40)

Observation time (days)	Group 2 (experimental, tRNA), n = 40				
	AsAT, U/L	AlAT, U/L	AP, U/L	Total bilirubin, μM/L	Total protein, g/l
Initial values	58 ± 8.0	40 ± 6.0	240 ± 24	2.2 ± 0.7	98 ± 20
2	423 ± 20*	276 ± 17*	987 ± 30*	7.9 ± 1.3*	48 ± 10*
3	383 ± 28*	108 ± 18*	632 ± 28*	6.5 ± 1.2*	52 ± 9.0*
5	238 ± 19*$^{\#}$	78 ± 10*$^{\#}$	460 ± 32*$^{\#}$	5.1 ± 1.1*$^{\#}$	54 ± 6.0*
7	115 ± 11*$^{\#}$	69 ± 6.2*$^{\#}$	346 ± 26*$^{\#}$	3.1 ± 1.0$^{\#}$	60 ± 7.0
10	82 ± 12$^{\#}$	58 ± 12$^{\#}$	257 ± 15$^{\#}$	2.7 ± 0.9	68 ± 8.0
14	66 ± 7$^{\#}$	44 ± 6$^{\#}$	230 ± 14$^{\#}$	1.9 ± 0.8	84 ± 12

Note. * – $p < 0.05$ compared to baseline; $^{\#}$ – $p < 0.05$ compared to control at the same time.

determined per 9678 cells, i. e., it was 5 times higher than in the control group).

On the 3rd day after the ELR modeling, MI in the study groups remained at a higher level compared to the baseline but changed compared to 48 hours: in the 1st, control group, MI decreased and amounted to 3.7‰, in the 2nd, the experimental group MI also decreased and amounted to 6.36‰. By the 5th day MI values in the 1st and 2nd groups approached the initial level and did not differ among themselves (Fig. 1).

From the obtained results of a comparative study of the mitotic activity of hepatocytes in the two studied groups, it follows that ELR itself induces the proliferative activity of hepatocytes, and the introduction of tRNA from BMC, already at an early stage, significantly enhances the proliferative activity of cells.

Higher mitotic activity of hepatocytes in group 2 (administration of tRNA) was accompanied by a significantly faster rate of liver weight recovery. In Fig. 2 shows the dynamics of liver weight recovery after ELR in the control and experimental groups.

From the presented graph it follows that a higher rate of liver weight recovery was noted in the experimental group, in which, 3–5 hours after ELR and intraperitoneal administration of tRNA, the recovery of liver weight occurred by 10–12 days.

In the control group with intraperitoneal saline injection, the restoration of liver mass occurred only on the 18th–20th day after ELR. Thus, the results obtained indicate that administration of tRNA at a dose of 30 μg/100 g of animal weight induces a more pronounced activation of regeneration processes in the liver after ELR. This can be explained by the fact that tRNA BMC is a ready-made complex of signaling RNA molecules

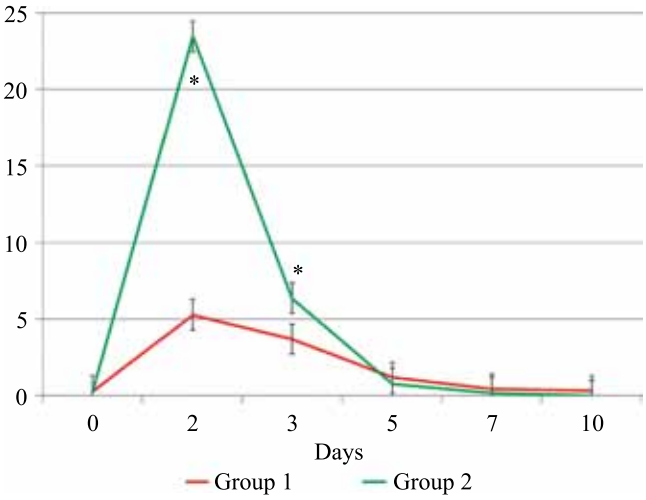

Fig. 1. Dynamics of changes in the mitotic index of hepatocytes in rat livers after ELR in the control (group 1 with the introduction of PS) and experimental (group 2 with the introduction of tRNA) groups. * – $p < 0,05$ compared to control at the same period

of various classes, which is able to penetrate into various cells freely and quickly, as well as be targeted by them (and their exosomes), especially with the help of blood mononuclear cells (lymphocytes) [9]. It is also important to note that when studying the dynamics of liver weight recovery after ELR in experiments with tRNA, the weight of the resected liver in the early stages (by day 2) was significantly less than the weight of the liver in the control group (Fig. 2).

If to consider the known facts that the process of liver regeneration after ELR at an early stage is accompanied by the phenomena of cellular autophagy [4, 5] and incre-

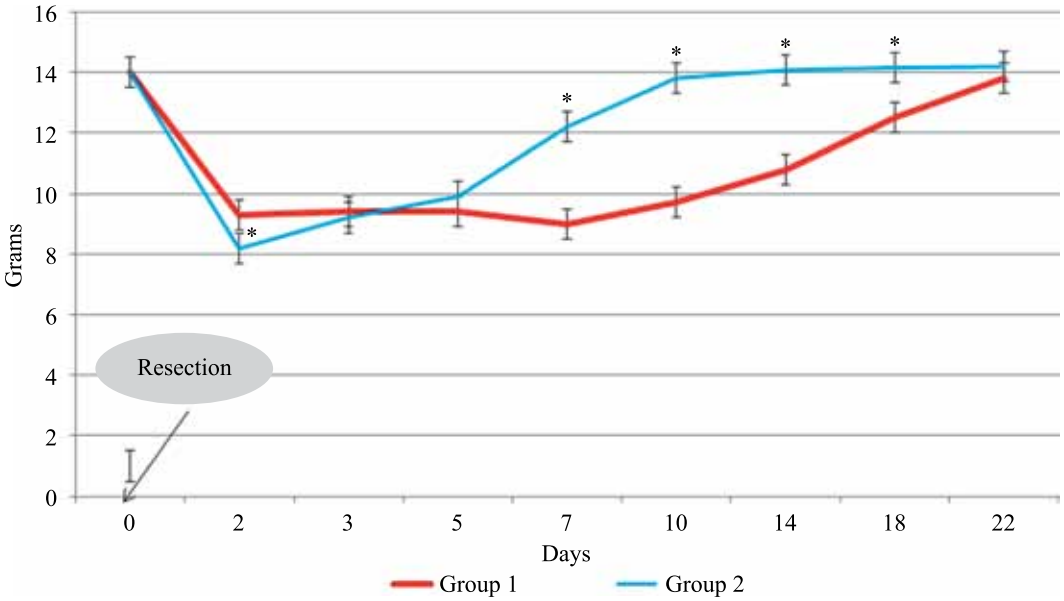

Fig. 2. Dynamics of the initial mass restoration of rat livers after ELR in the control (group 1 with the introduction of PS) and experimental (group 2 with the introduction of tRNA) groups. * – $p < 0,05$ compared to control at the same period

ased signs of reversible and even irreversible apoptosis of hepatocytes [6], the results obtained suggest that tRNA accelerates the process of restorative regeneration liver in comparison with the control due to a sharper and earlier (apparently, already within 1 day) and longer (within 2 days) intensification of manifestations of mobilization and consumption of its own cellular reserves (increased autophagy and apoptosis) with the development of NAS and the recovery process as a result of the combined effect on liver cells of two factors: ELR and tRNA.

Indeed, a comparative immunohistochemical study of Caspase-9 activity, an indicator of reversible apoptosis in liver cells of the control and experimental groups 48 h after ELR, i. e., at the height of activation of mitotic activity of hepatocytes, showed (Fig. 3, a and b) that both in the control and experimental groups, the process of reversible apoptosis was induced in more than 90% of hepatocytes. The study of Caspase-9 expression in liver cells of intact animals did not reveal the presence of this marker in them. The data obtained indicate an almost total activation in liver cells after ELR of adaptive-dependent apoptosis in the two study groups. However, in contrast to the control group, in the experimental group, the administration of tRNA led to a distinct increase in the mitotic activity of hepatocytes. This effect was also observed for hepatocytes, which emerged from the state of reversible apoptosis, since in mitotically dividing hepatocytes, the chromogen-stained substrate was washed out of the dividing nucleus and passed into the cytoplasm (Fig. 3, b). The results obtained indicate that the tRNA introduced into the body against the background of ELR, apparently, acts within the framework of the nonspecific adaptive syndrome of cellular systems as an adequate adaptogen, which turns on and optimizes the survival reserves of cells, switching evolutionarily programmed regulatory mechanisms in them from apoptosis to cell proliferation. The latter is possible if, in the early stages after ELR, the signals of apoptosis and proliferation in liver cells are in a co-activated state. According to I.M. Gazizov et al. [6], the intersection point of these signals can be the factors STAT-3 and NFK-β, with a significant increase in the levels and activities of which cells suppress apoptosis by expressing antiapoptotic proteins Bcl-2, Bcl-x1, HSP-70, G0-phases and enter into proliferation. The possibility of cell transition from the state of apoptosis to the phase of proliferation was also shown in [10].

It is known that the development of apoptosis is characterized by the occurrence of certain changes in the morphology of cells (the nucleus and cytoplasm decrease in size, condense without disrupting the structural integrity of cell membranes and the development of inflammation). To prove the development of adaptation-dependent apoptosis of liver cells in the early stages after ELR and active switching of cells from the proapoptotic pathway to the pathway of proliferation and regenerative regeneration using tRNA, a comparative morphometry of hepatocytes in the liver of rats from the control and experimental groups was carried out 48 hours after ELR, i. e. That is, at the time of maximum mitotic activity of hepatocytes. The results of the morphometric study of hepatocytes in the control and experimental groups, without and with the introduction of tRNA in comparison with intact animals (without ELR), are presented in Table 3 and 4. In the liver of rats of the control group, significant changes in the cytometric parameters of mononuclear and binuclear hepatocytes are observed. Thus, post-resection changes after 48 hours were characterized by a decrease in the areas of mononuclear hepatocytes, their nuclei and cytoplasm by 30.2; 34.0; 29.9%, respectively, and a decrease in these indicators for binuclear hepatocytes by 20.5; 35.0; 23.4% compared

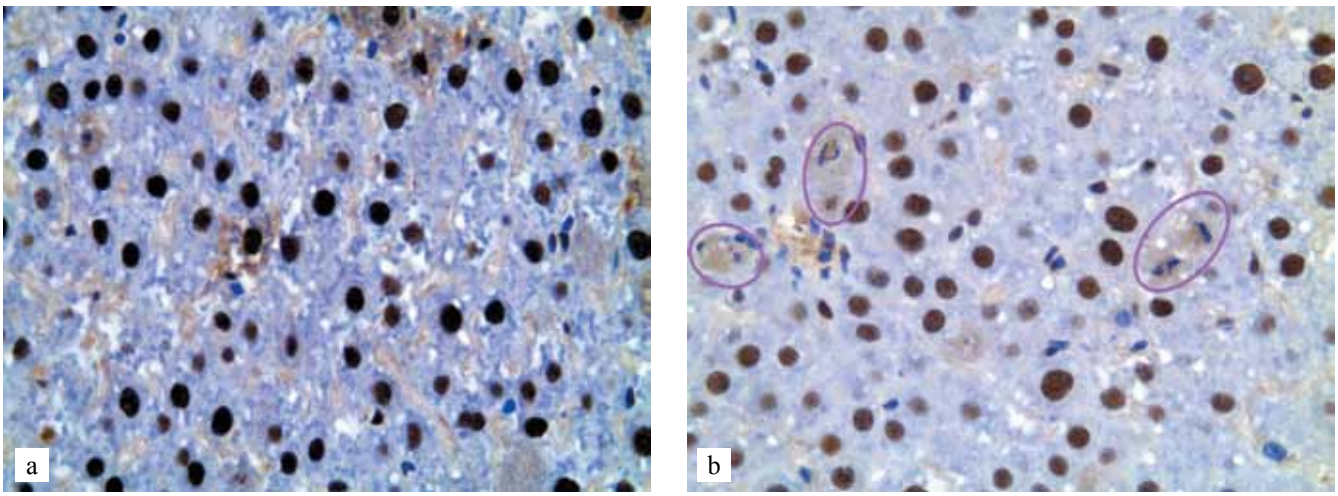

Fig. 3. Immunohistochemical investigation of Caspase-9 activity in hepatocytes in 48 hours after ELR in the control group with infusion of physiological saline (a) and in the experimental group with infusion of tRNA of BMCs (b). ×40. Cells in the mitosis phase are indicated by circles

Table 3

Changes in the cytometric indices of single- and double-nuclear hepatocytes in 48 hours after ELR without and with infusion of tRNA of BMCs (Me (Q1; Q2)) (median (25th, 75th percentiles)

Group / Parameter	Intact	Control group, saline	Experimental group, tRNA
Indicators of mononuclear hepatocytes			
Cell area, μm^2	318.7 (268.5; 378.4)	222.4 (174.1; 281.2)[1]	272.7 (219.4; 336.2)*
Nucleus area, μm^2	55.8 (50.0; 75.7)	36.8 (30.4; 41.9)[1]	45.6 (38.2; 52.2)*
Cytoplasm area, μm^2	262.6 (213.5; 309.4)	184.1 (141.6; 239.5)[1]	228.9 (179.7; 287.8)*
Indicators of binuclear hepatocytes			
Cell area, μm^2	420.1 (376.0; 489.2)	333.9 (279.0; 376.2)[1]	355.6 (293.0; 439.5)
Nucleus area, μm^2	100.1 (90.6; 108.9)	65.0 (53.5; 74.9)[1]	75.4 (60.2; 90.0)*
Cytoplasm area, μm^2	321.0 (286.0; 382.1)	261.1 (226.6; 307.5)[1]	276.8 (231.2; 341.8)

Note. [1] – the differences are significant ($p \leq 0.01$) compared with the intact group; * – the differences are significant ($p \leq 0.01$) compared to the control group of rats with ELR; area – average area.

Table 4

Change in the total number of hepatocytes per unit area and the percent of single- and double-nuclear cells in 48 hours after ELR without and with infusion of tRNA (M ± m)

Group / Parameter	Intact	Control group, saline	Experimental group, tRNA
Total number of cells per 50000 μm^2	78.4 ± 4.9	100.8 ± 9.2[1]	95.2 ± 5.7
Mononuclear cells, %	87.43 ± 0.95	92.70 ± 0.75[1]	91.81 ± 0.40
Binuclear cells, %	12.57 ± 0.95	7.30 ± 0.75[1]	8.19 ± 0.40

Note. [1] – differences are significant ($p \leq 0.01$) compared with an intact group.

with hepatocytes in the liver of an intact group of rats. There was also a statistically significant decrease in the number of binucleated hepatocytes by 5.27% against the background of an increase in the total number of cells per unit area by 27.3% (Table 4).

For the liver of the experimental group, intraperitoneal administration of tRNA led to a change in all investigated cytometric parameters of mononuclear hepatocytes, and to a lesser extent influenced the parameters of binuclear hepatocytes. Thus, with the introduction of tRNA, an increase in the areas of mononuclear hepatocytes, their nuclei and cytoplasm were observed by 22.6; 23.9 and 24.3%, respectively, compared with the control group. At the same time, no changes were found in the number of binuclear cells (Table 4), but an increase in the area of the nuclei of binuclear hepatocytes was observed by 15.5% in comparison with the control group (Table 3).

The results of morphocytometry of hepatocytes 48 hours after ELR in the control group suggest that under conditions of almost total activation of Caspase-9 (more than 90% of hepatocytes) and not a pronounced increase in the proliferative activity of hepatocytes (mitotic index – 5.37‰), an increase in cell density, as well as a general decrease in the areas of hepatocytes, their nuclei, and cytoplasm indicates, first of all, a predominant increase in the processes of autophagy and reversible apoptosis in liver cells in the early stages after ELR. The observed decrease in the number of binucleated cells in the liver of the control group of rats may be associated with their division and the formation of mononuclear cells [11].

Administration of BMC tRNA 48 hours after ELR retains the high level of Caspase-9 activity in hepatocytes unchanged. There is a sharper decrease in the mass of the resected liver at this time in comparison with the control group as a result of stress effects of ELR and tRNA. At the same time, in the liver, the mitotic activity of hepatocytes sharply increases (MI = 23.45‰) and a reliable recovery of morphometric parameters begins (an increase in the areas of nuclei, cells, and cytoplasm in comparison with the control group) of predominantly mononuclear hepatocytes, which, apparently, are capable of more more actively than binuclear hepatocytes, to proliferate and hypertrophy in critical situations. At the same time, the persisting higher cell density per unit area against the background of the use of tRNA also indicates the continuing apoptosis of cells during the study period.

The property of tRNA proved on the experimental model of ELR to simultaneously maintain apoptosis processes in liver cells and induces mitotic activity in them indicates that tRNA is able to switch activated apoptosis to cell proliferation at the early phase of the regeneration process. The observed effect is most likely due to the presence of regulatory RNA molecules, including numerous protein-noncoding RNAs [12–14], which are actively involved in regeneration processes and are part of the BMC tRNA.

CONCLUSION

The results obtained allow us to conclude that tRNA, used for the induction of recovery processes in the liver, promotes at the cellular level the activation of early manifestations of the evolutionarily developed nonspecific adaptive mechanism of cell survival, while simultaneously supporting signaling pathways in them, apoptosis, and proliferation in a co-activated state and also induces the transition of cells from adaptive-dependent apoptosis to proliferation by expressing anti-apoptotic proteins, the genes of which are the targets of numerous regulatory RNA molecules that make up BMC tRNA.

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The authors declare no conflict of interest.

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