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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Migration, proliferation and cell death of regenerating liver macrophages in an experimental model

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Abstract. Relevance. Macrophages are the leading regulatory cell-lineage taking part in reparative processes in mammals, and the liver is no exception. The ratio of monocyte migration, proliferation and death of macrophages during liver regeneration requires further studies. *The aim* was to quantify the intensity of monocyte migration, cell proliferation and apoptosis of resident liver macrophages after its 70 % resection in a mouse model. *Materials and Methods.* We performed 70 % liver resection in sexually mature male BalbC mice. Cells of liver monocyte-macrophage system were obtained by magnetic sorting by marker F4/80. The immunophenotype of the isolated cells was further studied by cytofluorimetry, the level of proliferation and cell death, the content of cyclins and P53 was determined by western blot. *Results and Discussion.* It was found that after partial hepatectomy there is a marked migration of monocytes/macrophages positive for Ly6C and CD11b markers to the liver, the migration process starts already in the first day after the operation. On the same terms there is a rise in proliferative activity of macrophages, established by Ki67 marker, the peak of proliferation — 3 days after partial hepatectomy. A significant increase in the number of dying macrophages was found early after liver resection. *Conclusion.* The obtained data indicate that liver regeneration in mammals on the model in mice is accompanied by proliferation migration and cell death of macrophages. Taking into account the immunophenotype of macrophages, we can conclude that Ly6C+ blood monocytes migrate to the liver, and resident macrophages participate in proliferation. The obtained data confirm the universality of the course of reparative processes in mammals.

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Introduction

Regeneration is an inherent property of all living organisms. Considering the regenerative ability of animals, it is possible to pay attention to the fact that it acquires the most diverse forms in the course of phylogenesis. However, despite the differences in the course of the regenerative process in different animals, many similar features are also identified: activation of similar signaling pathways, the presence of cell dedifferentiation/transdifferentiation, proliferation and cell death [1]. An integral part of the regeneration process in highly organized multicellular animals is the involvement of macrophages [2–4]. Given the large number of similarities, many researchers have suggested that the regenerative capacity in animals is homologous [1, 5].

The liver is characterized by a significant capacity for regeneration. At the same time, the reparative process in the liver is characterized by the same features as regeneration in other classes of animals: activation of signaling pathways regulating the processes of liver

development and growth, activation of cell death, cell proliferation, and, in case of viral or toxic damage, cell transdifferentiation processes [6].

A huge role in the regulation of liver regeneration is attributed to macrophages, which is the subject of many studies [7]. Two types of models are usually used to study liver regeneration: after parenchyma resection and after toxic damage. The population of liver macrophages has been characterized in the most detail in the reparative process after toxic damage [8, 9]. It has been shown that monocytes migrate to the liver during toxic damage, and both migrating monocytes and macrophages formed from them and resident macrophages (Kupffer cells) are necessary for reparative processes [8, 9].

Data on the role of macrophages of medullary origin in mammalian liver regeneration after resection are contradictory [10]. Some studies indicate the absence of migration of medullary macrophages in the liver after removal of part of the parenchyma [11–13], while others show such a possibility [14, 15].

The aim of this work was to quantify the intensity of monocyte migration, proliferation and cell death of resident liver macrophages after its 70 % resection in a mouse model.

Materials and methods

Animals

Male mice of the BalbC line, weight 20–22 g, obtained from the «Stolbovaya» animal nursery (Chekhov, Moscow region, Russia) were used. The animals were kept in standard vivarium conditions. The conditions of laboratory animals were in accordance with the «International recommendations for conducting biomedical research using animals» of 1985, the rules of laboratory practice (Order of the Ministry of Health of Russian Federation 16.06.2003 № . 267), the Geneva Convention «International Guiding Principals for Biomedical Involving Animals» (Geneva, 1990), as well as the European Convention for the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes (Strasbourg, 1986).

Experimental model

In mice (n = 76), a 70 % resection was performed under general isoflurane anesthesia according to the method of Higgins and Anderson [16]. The surgery was performed from 10.00 p.m. to 11.00 p.m. Animals

were removed from the experiment after 0h, 24h, 72h and 7 days. Intact (n = 25) as well as falsely operated animals (n = 27) were used as controls. The study was approved by the bioethics commission of the FGBNU Research Institute of Human Morphology (Protocol no. 3, dated 01.02.2019).

Kupffer cell isolation

Kupffer cells were isolated on a MidiMACS™ Separator magnetic sorter using LS Columns (Miltenyi Biotec, Germany) and Anti-F4/80 MicroBeadsUltraPure magnetic microparticles (Miltenyi Biotec, Germany) according to the manufacturer's recommendations.

Flow cytometry analysis

The isolated macrophages were prepared for staining using InsideStainKit (Miltenyi Biotec, Germany). The antibodies used and the corresponding serotypic controls are summarized in Table 1. Antibodies were selected to assess the purity of the cells obtained by cell sorting — pan-macrophage marker F4/80 (cell adhesion protein) was used, as well as monocytic (bone marrow origin) macrophage markers — CD11b (integrin alpha-M involved in adhesion and endocytosis), Ly6C — a protein thought to be essential for monocyte migration. The analysis was performed on a Cytomics FC 500 cytometer (BeckmanCoulter, USA).

Table 1

Antibodies for flow cytometry

Antibodies	Isotypic control	Isotypic control
CD11b-VioBright FITC, mouse (clone: REA592)	REA Control-VioBright FITC	Miltenyi Biotec
Ly-6C-PE, mouse	Rat IgG2a-PE	Miltenyi Biotec
Anti-F4/80-PerCP-Vio700, mouse	REA Control-PerCP-Vio700	Miltenyi Biotec
Ki67-PE, anti-human/mouse, REAfinity™	REA Control Antibody (I), human IgG1, PE, REAfinity™	Miltenyi Biotec

Proliferative activity of macrophages

Proliferation activity was determined using Ki67 marker. Appropriate antibodies and isotypic control for flow cytometry are listed in Table 1.

Cell death activity

The level of cell death was examined by flow cytometry using the ANNEXIN V — FITC Kit — Apoptosis Detection Kit (Beckman Coulter, USA).

Western blot analysis

The amount of protein was determined by Western blotting according to the previously described method [11]. Proteins were isolated using MicroRotoforCellLysiskit (Bio-Rad Laboratories, Inc., USA). Proteins were transferred to membranes using Trans-Blot® Turbo™ RTA Mini LF PVDF TransferKit (Bio-Rad Laboratories, Inc., USA). Membranes were stained with first antibodies at a dilution of 1:100 (Abcam, UK). Then with second antibodies conjugated to horseradish peroxidase Immun-StarGoatAnti-Rabbit (GAR)-HRP Conjugate (Bio-Rad Laboratories, Inc., USA). The stained membranes were analyzed using ImageLab (Bio-Rad Laboratories, Inc., USA).

Statistical analysis

The results were analysed in SigmaStat 3.5 software (Systat Software Inc., USA), using ranked one-factor analysis of variance with post-hoc analysis. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

Immunophenotype of macrophages of regenerating liver

The phenotype of isolated macrophages from both intact and resected liver was studied, and it was found that 88.6 ± 6.2 % of cells carried the F4/80+ marker, approximately 4.7 ± 0.96 % of cells expressed Ly6C, 5.4 ± 1.0 % of cells were CD11b+(Fig.1 A, B). These results indicate that under normal conditions, the mouse liver macrophage population is represented almost exclusively by resident macrophages, Kupffer cells.

Liver resection markedly affected the immunophenotype of its macrophages. The greatest changes concerned the cells expressing CD11b and Ly6C. The number of Ly6C+ cells in the liver significantly increased 1 day after resection (11.7 ± 1.2 %) and increased up to 7 days after the operation (22.25 ± 1.3 %). Similar dynamics was observed in CD11b+ cells: there was a sharp increase by 3 days after resection (74.5 ± 1.1 %), by 7 days the number of CD11b+ cells decreased, but remained above the control value (Fig.1 A, B). The participation of

macrophages in regeneration is a highly conserved cellular mechanism of reparative processes, which is indicated by comparative studies conducted on representatives of several classes of vertebrates [4, 17].

As a rule, many macrophages of monocytic (medullary) origin migrate to the damaged organ during regeneration [4]. However, under normal conditions, the mammalian liver contains the most numerous population of macrophages, including those leading their origin from erythro-myeloid precursors of the yolk sac wall. At the same time, different authors in the study of liver regeneration have used markers that are expressed to a greater or lesser extent by both resident macrophages and those of bone marrow origin [14], or markers that are present not only in monocytes but also in other cells of the myeloid lineage [15]. In this regard, for a long time, due to the lack of specific markers reflecting the origin of macrophages, it was problematic to reliably estimate the extent of macrophage migration to the liver.

A great number of studies on mammalian liver regeneration have been performed on the model of 70 % liver resection. Due to the absence of a pronounced alteration phase in such damage, the question of the participation of macrophages of medullary origin in liver regeneration after resection remains debatable and poorly studied [11–14].

Based on the dynamics of Ly6C+ cells established in our study, we can conclude that a large number of monocytes/macrophages of medullary origin migrate into the regenerating liver after 70 % resection. The findings are in general agreement with those of Nishiyama et al. (2015), in which bone marrow-derived macrophages were detected using the marker CD11b [14]. At the same time, we found that the proportion of CD11b+ cells out of the total number of isolated F4/80+ cells on the 3rd day after resection reached 70 %, which exceeds the number of Ly6C+macrophages on the 3rd day. One of the reasons for this phenomenon may be the change in the level of CD11b expression in resident liver macrophages under the influence of LPS [14,19]. The migration of granulocytes (eosinophils and neutrophils) into the regenerating liver together with monocytes/macrophages of bone origin cannot be excluded, which is important for mammalian liver regeneration [19].

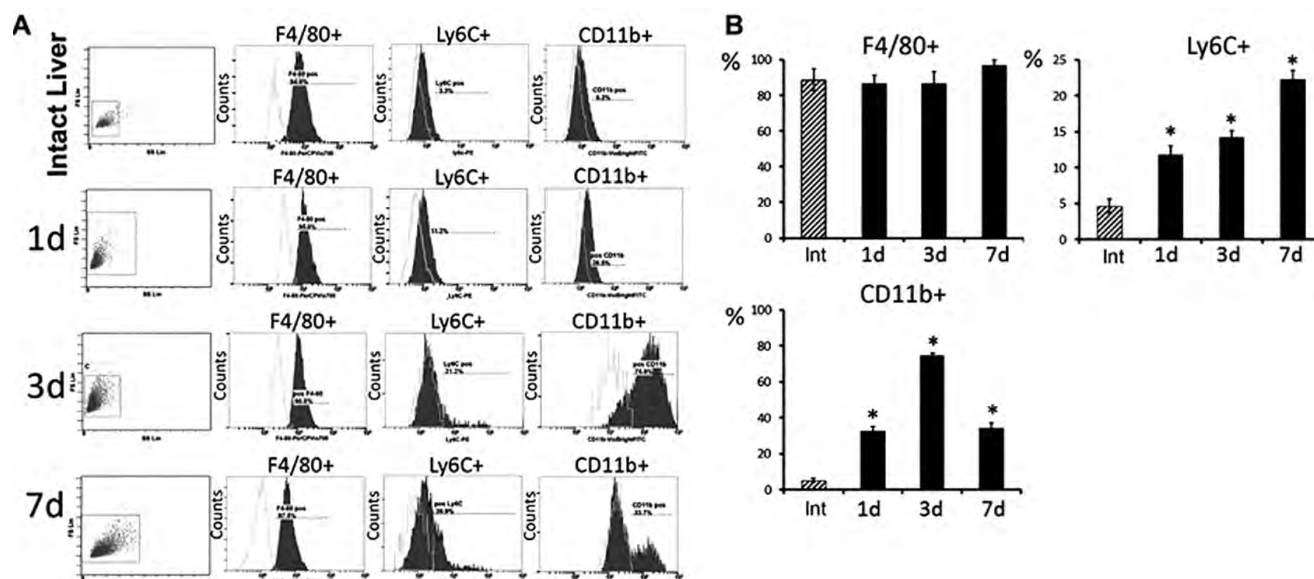


Fig. 1. Immunophenotype of macrophages in the regenerating liver according to flow cytometry. The abscissa axis shows the timing of liver regeneration (days); the ordinate axis shows the proportion of macrophages expressing the marker under study (%). Data are presented as mean values \pm standard deviation, * – $p < 0.05$ statistically significant differences relative to intact control (Int)

Proliferation dynamics

When studying the level of proliferation dynamics using Ki 67 marker in the liver after 70 % resection it was found that statistically significant increase of Ki67+ macrophages was observed 1 day after resection, the highest value of this index was reached 3 days after the operation ($36,9 \pm 5,9$ %), significantly increased number of Ki67+ macrophages remained till 7 days after the operation (Fig. 2 A). At the same time, the content of Cyclin D1 protein in macrophages of regenerating liver did not change, and the level of Cyclin E protein was statistically significantly increased 7 days after liver resection (Fig. 2B).

In addition to migration, the number of macrophages in the reparative process depends on the level of their proliferation and cell death. The model of Th2-inflammation of the peritoneum caused by the nematode *Litomosoides sigmodontis* invasion is an example of the extreme expression of the proliferation contribution to the increase in the number of macrophages [20]. In the same study,

it was noted that even under physiologic normal conditions, a significant proportion of resident peritoneal macrophages are in the mitotic cycle [20]. Macrophage proliferation plays a significant role in reparative processes in the liver as well. On the model of mice liver damage by paracetamol it was also established that exactly resident macrophages were characterized by the expressed proliferative ability in comparison with monocyte-derived macrophages, and the peak of macrophage proliferation in the conditions of this model is noted on the 3rd day [8]. It is believed that in rats after 70 % resection the peak proliferation of resident macrophages is noted after 2 days [21], similar data were obtained in conditions of liver resection of more than 80 % [11]. It is known that in mice hepatocyte proliferation during liver regeneration after resection starts later compared to other laboratory animals [22]. Our data are in agreement with this: the peak of macrophage proliferation is observed on the 3rd day after liver resection [8].

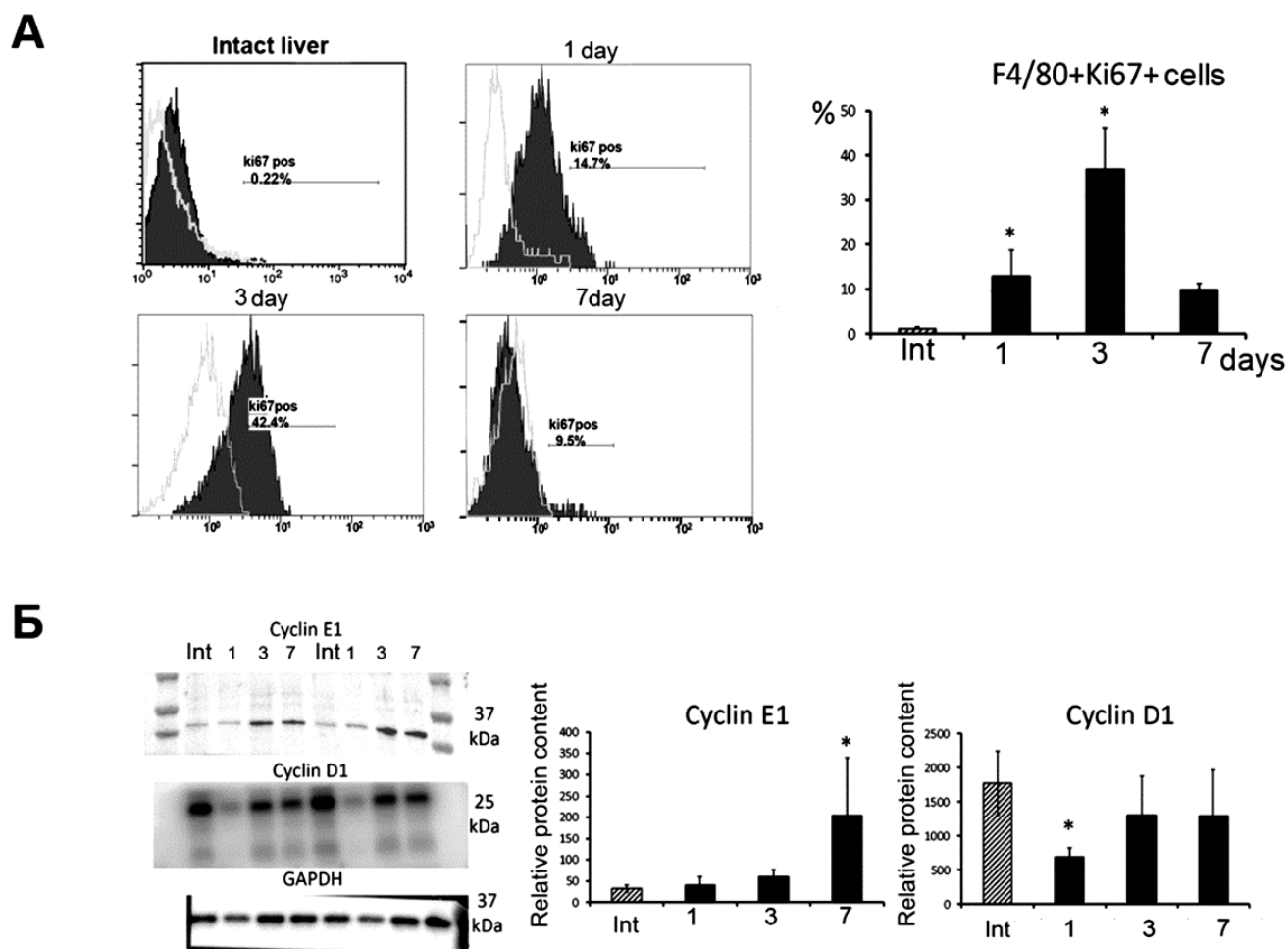


Fig. 2. Proliferation activity (A), relative content of factors regulating the proliferation of macrophages in the regenerating liver (B). On the abscissa axis is the timing of liver regeneration (days), on the ordinate axis is the proportion of macrophages expressing the marker under study (%) or the relative level of protein. Data are presented as mean values \pm standard deviation, * – $p < 0.05$ statistically significant differences relative to the intact liver (Int)

Cell death of macrophages of regenerating liver

Macrophages dying by apoptosis are found in the liver mainly only 1 day after surgery, the number of PI+ AnnexinV+ was about 11 %, and then sharply decreased (Fig. 3A). Meanwhile, a decrease in p53 protein levels in macrophages was observed after liver resection in mice (Fig. 3B).

The timing of the increase in the apoptosis activity of liver macrophages after 70 % resection is consistent with toxic models of liver injury [8], indicating, first of all, that it is the resident liver macrophages that die after liver resection.

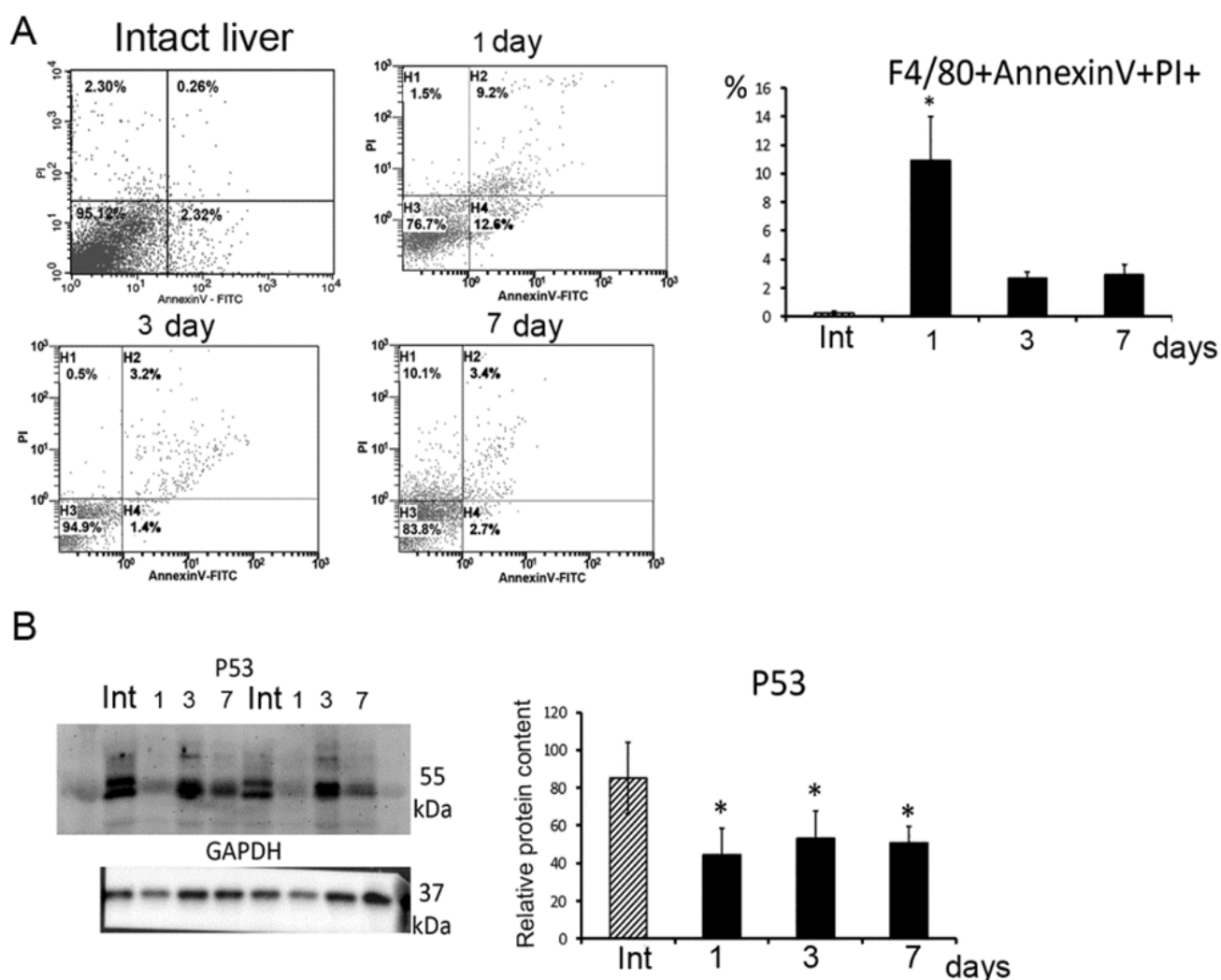


Fig. 3. Cell death activity (A), relative content of factors regulating cell death of macrophages in the regenerating liver (B). On the abscissa axis is the timing of liver regeneration (days), on the ordinate axis is the proportion of macrophages expressing the marker under study (%) or the relative level of protein. Data are presented as mean values \pm standard deviation, * – $p < 0.05$ statistically significant differences relative to the intact liver (Int)

Conclusion











The obtained data testify to the universality of the course of reparative processes in mammals regardless of their localization, as it was found that liver resection causes migration of Ly6C+CD11b+ monocytes into the damaged organ, activation of proliferation and death of resident macrophages. The loss of resident macrophages is restored by their proliferation.

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Миграция, пролиферация и клеточная гибель макрофагов регенерирующей печени в экспериментальной модели


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Аннотация. Актуальность. Макрофаги — ведущий клеточный дифферон, принимающий участие в регуляции репаративных процессов у млекопитающих, не является исключением и печень. Соотношение миграции моноцитов, пролиферации и гибели макрофагов при регенерации печени требует дальнейших исследований. Цель исследова-

ния — количественно оценить интенсивность миграции моноцитов, клеточного размножения и апоптоза резидентных макрофагов печени после ее 70 % резекции на модели у мыши. *Материалы и методы.* Выполняли 70 % резекцию печени у половозрелых самцов мышей линии Balb C. Клетки моноцитарно-макрофагальной системы печени получали с помощью магнитного сортирования по маркеру F4/80. Далее изучали иммунофенотип выделенных клеток с помощью цитофлуориметрии, уровень пролиферации и клеточной гибели, содержание циклинов и P53 определяли методом вестерн-блот. *Результаты и обсуждение.* Установлено, что после частичной гепатэктомии наблюдается выраженная миграция моноцитов/макрофагов положительных по маркерам Ly6C и CD11b в печень, процесс миграции начинается уже в первые сутки после операции. На этих же сроках отмечается подъем пролиферативной активности макрофагов, установленный с помощью маркера Ki67, пик пролиферации — 3 сутки после частичной гепатэктомии. В ранние сроки после резекции печени обнаружено значимое увеличение числа гибнущих макрофагов. *Выводы.* Полученные данные свидетельствуют о том, что регенерация печени у млекопитающих на модели у мышей сопровождается миграцией, пролиферацией и клеточной гибелью макрофагов. Учитывая иммунофенотип макрофагов, можно заключить, что в печень мигрируют Ly6C+ моноциты крови, а в пролиферации участвуют резидентные макрофаги. Полученные данные подтверждают универсальность течения репаративных процессов у млекопитающих.

Ключевые слова: печень, регенерация, макрофаги, миграция, пролиферация, апоптоз

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