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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ

Macrophage population state and proliferative activity of spleen cells under liver regeneration conditions

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Abstract. Relevance. Currently, the participation of immune system cells in the regulation of reparative processes is attracting more and more attention of researchers. There is an anatomical connection between the liver and spleen by means of portal vein. Thus, cytokines and other biologically active substances can enter the liver from the spleen through the portal vein, as well as cells can migrate to the liver. However, the specific mechanisms of mutual influence of the mentioned organs, including in reparative processes, remain poorly studied. *The aim* of our work was to study the state of spleen monocyte-macrophage population after liver resection, as well as the proliferative activity of spleen cells during liver regeneration. *Materials and Methods.* The model of liver regeneration after 70 % resection in mouse was reproduced in this work. The animals were taken out of the experiment after 1, 3 and 7 days. The marker of cell proliferation Ki67 was immunohistochemically detected, the state of spleen monocyte-macrophage population was evaluated by markers CD68, CD115, CD206, F4/80 by methods of immunohistochemistry and flow cytometry. *Results and Discussion.* The liver regeneration had a pronounced effect on the cytoarchitectonics of the spleen. In 1 day after liver resection in the spleen there was observed a decrease in the share of Ki67+cells, according to the flow cytometry data there was a decrease in the number of CD115+cells, in 3 and 7 days there was a decrease in the number of F4/80+ macrophages. *Conclusion.* Liver resection causes changes in the state of cell populations of the spleen as well. First of all, to the decrease in the activity of proliferative processes in it, as well as to the changes in the state of the monocyte-macrophage system. A decrease in the content of CD115+ and F4/80+ cells in the spleen was found, which indirectly indicates the migration of monocytes/macrophages after liver resection, which can also influence the course of reparative processes in the liver.

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Introduction

The immune system together with the nervous and endocrine systems belongs to the regulatory systems of the mammalian organism. Nowadays, the participation of immune system cells in the regulation of reparative processes is attracting more and more attention of researchers. There is a direct anatomical connection between some immune and non-immune organs. Therefore, mutual influence and coordinated changes in the development of pathological and reparative processes often attract attention. First of all, we are talking about the interaction between the spleen and the liver within the framework of the so-called hepatic-spleen axis [1]. The basis of this interaction is the portal circulation linking the spleen and liver, as well as the presence of common barrier and immune functions [1]. Despite the direct connection of the liver and spleen, the specific mechanisms of mutual influence of these organs, including reparative processes, remain poorly understood [2].

Most studies of the hepatic-spleen axis have been performed in patients with liver cirrhosis of various etiologies or on appropriate models in laboratory animals. In this regard, special attention was paid to the factors of liver Ito cell activation, which are responsible for the excessive production of intercellular substance components [3]. It has been found that during the development of hepatitis and cirrhosis both in experiment [4] and in patients [5] there is an activation of TGFb1 synthesis by macrophages of the red pulp of the spleen, which reaches the liver through the portal vein, where it activates Ito cells (hepatic stellate cells). In other works, on the contrary, the potential possibility of favorable influence of spleen on reparative processes in the liver is shown. Thus, it was found that in the spleen there is an increase in gene expression of a number of interleukins, as well as hepatocyte growth factor HGF after liver resection [6, 7]. Probably, the spectrum of biologically active substances synthesized in the spleen is much wider in the spleen after liver resection; however, this issue remains poorly studied.

In addition to being a source of synthesis of cytokines and growth factors regulating inflammation and reparative processes, the spleen can also serve as a source of migrating cells. Currently, there is evidence that the spleen deposits monocytes, from where they migrate to the focus of damage, which was shown in the model of ischemic myocardial and brain damage [8, 9].

It is well known that monocytes/macrophages as well as other leukocytes migrate to the liver after it has been damaged by toxic substances or resection [10–12]. There are no data on the role of the spleen in this process, as well as there are no studies on the state of the monocyte/macrophage population of the spleen during liver regeneration. Purpose of research: based on the given data, the interaction between the spleen and the liver after its resection remains poorly studied. Thus, the aim of our work was to study the state of spleen monocyte-macrophage population after liver resection, as well as the proliferative activity of spleen cells during liver regeneration.

Materials and methods

Animals

Male mice of the C57Bl line, weight 20–22 g, obtained from the animal nursery «Stolbovaya» (Chekhov, Moscow region, Russia) of the Federal State Budgetary Institution of Science «Scientific Center for Biomedical Technologies of the Federal Medical and Biological Agency» were used. Animals were kept in plastic cages at 22 ± 1 °C under natural light with free access to standard food for laboratory rodents and water. The conditions of laboratory animals were in accordance with the USSR Ministry of Health Order No. 755 of 12.08.1977 and the European Convention for the Protection of Vertebrate Animals Used for Experiments or Other Scientific Purposes (Strasbourg, March 18, 1986).

Experimental model

In male C57bl/10 mice ($n = 18$), a 70 % resection was performed under general isoflurane anesthesia according to the method of Higgins and Anderson [13]. The operation was performed from 10.00 p.m. to 11.00

p.m.p.m. Animals were removed from the experiment after 24h, 72h and 7 days using CO₂-chamber. Intact ($n = 6$) as well as falsely operated animals ($n = 15$) were used as controls. All experiments were performed in accordance with the Geneva Convention «International Guiding Principles for Biomedical Involving Animals» (Geneva, 1990), as well as the Helsinki Declaration of the World Medical Association on Humane Treatment of Animals (edition of 2000) The study was approved by the Bioethics Commission of the FGBNU Research Institute of Human Morphology (Protocol no. 29 (5), dated 08.11.2021).

Immunohistochemical study

Spleen fragments were rapidly frozen in liquid nitrogen, then cryosections were prepared and incubated with the first antibodies for 12 h, then for 1 h with the corresponding second antibodies conjugated with fluorophores (FITC or PE) (1:200, Abcam, UK). Antibodies against Ki67 (1:100, Abcam, UK) were used to examine cell proliferation, and antibodies against CD68 (1:100, Abcam, UK), against CD163 (1:100, Abcam, UK), and against CD206 (1:100, Abcam, UK) were used to detect the macrophage population. nuclei were dock-stained with 4',6-diamidino-2-phenylindole (DAPI, Sigma-Aldrich Co LLC). On cryosections stained with one or another antibody, an index of the corresponding positively stained cells was determined as the ratio of labeled cells to the total number of cells studied. For each index at least 3000 cells were studied, the index value was expressed in %.

Flow cytometry analysis

In animals removed from the experiment, the spleen was removed and placed in Hanks' solution (PanEco, Russia). The organ was washed twice with Hanks' solution. The leukocyte fraction was separated from the stromal fraction using a 40 µm nylon filter (SPL LifeScience, South Korea). Spleen tissues were mechanically disaggregated, minced and incubated in 0.05 % solution of collagenase cocktail of types 1 and 4 (PanEco, Russia) for 25 min at 37 °C on an orbital shaker. The resulting cell suspension was passed through a 100 µm nylon filter (SPL LifeScience, South Korea)

and was washed twice from enzymes in Hanks' solution containing 10 % fetal calf serum (PAA Lab., Austria) (500 g, 10 min, 20 °C). Erythrocytes were then lysed with Red Blood Cell Lysis Solution (Miltenyi Biotec, Germany) according to the manufacturer's protocol.

Immunophenotyping of the obtained cells was performed according to the following markers: Ly6C, F4/80, CD115. Cells were incubated with antibodies according to the manufacturer's protocol. Cells were then washed in PBS, resuspended in 0.3 ml PBS and transferred to flow cytometry tubes for analysis on a BD FACSAria III instrument (Becton Dickinson, USA). At least 10,000 cells were analyzed in each measurement.

For immunophenotyping of macrophages, a number of markers reflecting one or another of their functions have been selected. Ly6C, a protein thought to be essential for monocyte migration, CD115 is a receptor for M-CSF. CD68 (macrosialin) is a key protein involved in endocytosis, recognizes lectins and selectins, which allows the macrophage to move on selectin-containing surfaces, including the surface of other cells [14]. CD163 scavenger receptor of hemoglobin-haptoglobin complexes, is also able to bind to bacteria [15]. CD206 receptor recognizes terminal residues of mannose, N-acetylglucosamine and fucose on glycans attached to proteins of some microorganisms, anti-inflammatory function includes binding and removal from the bloodstream of glycoproteins released during inflammation (hydrolases, tissue plasminogen activator, neutrophil myeloperoxidase) [16].

Statistical analysis. The obtained data were analyzed using SigmaStat 3.5 software (Systat Software Inc., USA). Comparison of two samples was performed using the Mann-Whitney (U) criterion. For comparison of more than two groups, a ranked one-factor analysis of variance was used. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion

The hepatic-spleen axis of interorgan interaction was first discovered and studied in developing liver fibrosis. In such conditions, removal of the spleen, as a rule, had a favorable effect on the liver — a decrease

in the severity of fibrotic changes was noted [1, 17]. The following mechanism was supposed. During the development of hepatitis of various etiologies and subsequent fibrosis there is a permanent death of hepatocytes. Their decay products get into the systemic bloodstream and reach the spleen, where they stimulate the secretion of various cytokines and growth factors, primarily those that support a high level of inflammation and excessive formation of connective tissue in the liver [4, 5]. Cytokines synthesized in the spleen reach the liver through the portal vein and cause a new wave of cell death of hepatocytes. Thus, the circle is closed. Splenectomy removes the source of cytokines damaging the liver, thus breaking the vicious circle [2].

However, the effect of the spleen on the liver is not so unambiguously negative. Liver resection led to changes in cytoarchitectonics of the spleen. First of all, liver resection led to a statistically significant decrease in the proliferative activity of spleen cells. The decrease in the number of Ki67+ cells was observed both in the red and white pulp. The proliferative activity in the red pulp significantly decreased 1 day after liver resection, 3 and 7 days after the operation did not differ from the control values (Figure 1). In white pulp there was a longer decrease in the number of Ki67+ cells, proliferative activity returned to control values only by 7 days (Figure 1). Probably, liver resection has a depressing effect on hematopoiesis in the spleen, in connection with which defense mechanisms are activated in it [18].

Liver resection resulted in changes in the monocyte-macrophage population in the spleen. When analyzing histological preparations, it can be noted that CD68+ cells are localized in the red pulp, as well as CD163+ cells, while CD206+ cells are associated mainly with lymphoid nodules. This distribution of macrophages is characteristic of both the spleens of control and experimental animals. Liver resection did not significantly affect the topography of the indicated types of macrophages. Only 1 day after liver resection, one can note an increase in the number of CD206+deprived lymphoid nodules. In case of CD163+ cells, 1 day after liver resection, staining with appropriate antibodies gave brighter glowing.

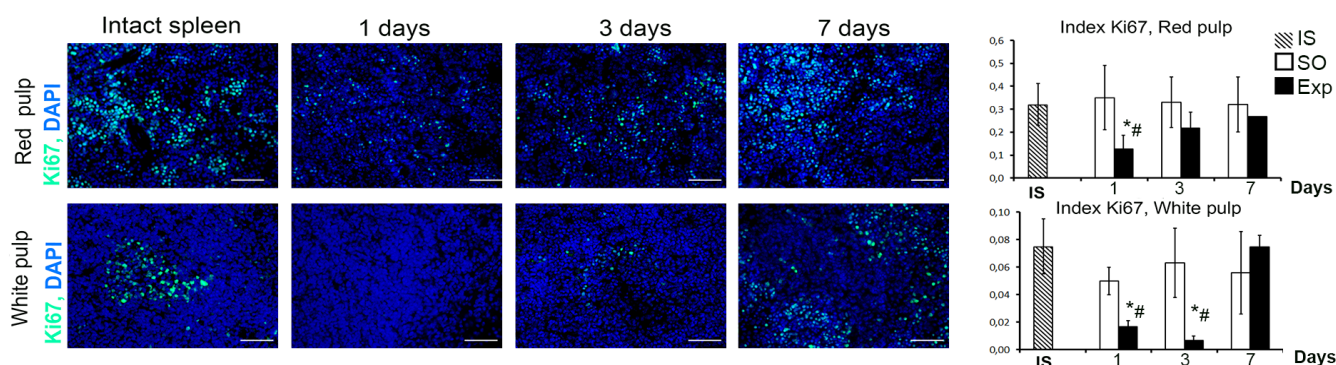


Fig. 1. Cell proliferation activity in the spleen during liver regeneration after 70 % resection. IS – intact spleen, SO – sham-operated control, RP – spleen of animals in which liver resection was performed, scale bars – 50 μ m, diagrams show average values \pm st. deviation, * – statistically significant difference compared to sham-operated control ($p < 0.05$), # – statistically significant difference compared to intact control ($p < 0.05$)

The study using flow cytometry revealed significant changes in the population of spleen macrophages in response to liver resection. It was found that in the total spleen cell population the number of CD115+ cells was significantly lower compared to the control only after 1 day, Ly6C+ cells throughout the study period, and F4/80+ cells at 3 and 7 after liver resection (Figure 2).

Similar data were obtained in those studies showing migration of deposited monocytes from the spleen into damaged organs [8, 9]. Thus, it can be assumed that during liver regeneration the monocytes migrating to the liver were also deposited initially in the spleen.

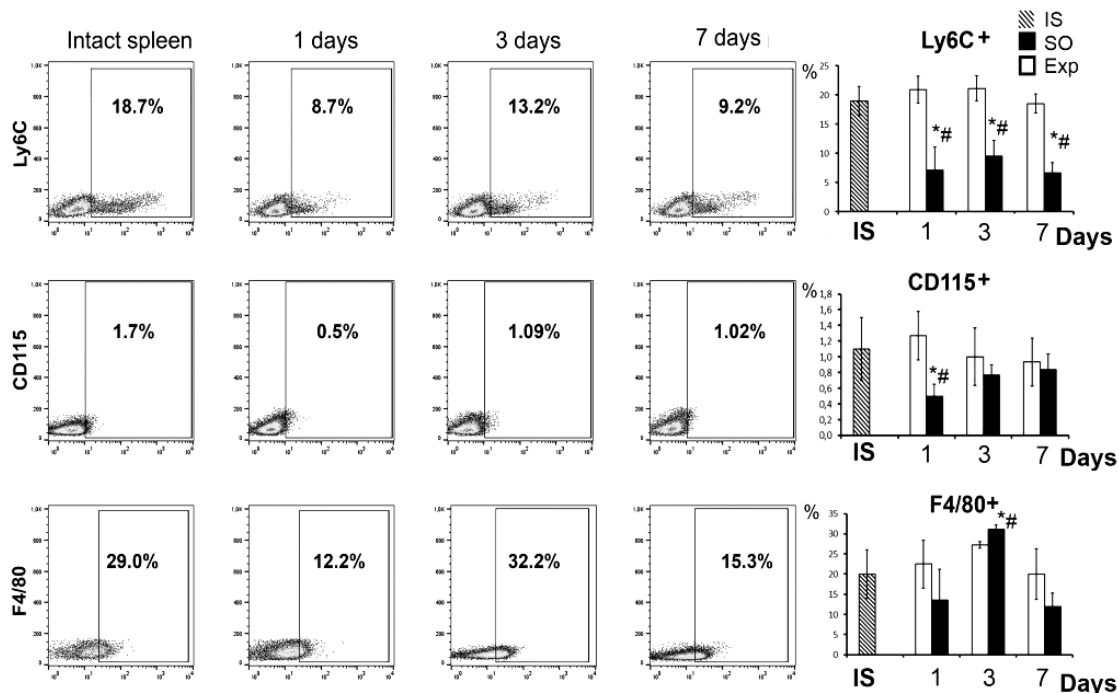


Fig. 2. The state of the monocyte-macrophage system in the spleen during liver regeneration after 70 % resection. IS – intact spleen, SO – sham-operated control, RP – spleen of animals in which liver resection was performed, scale bars – 50 μ m, diagrams show average values \pm st. deviation, * – statistically significant difference compared to sham-operated control ($p < 0.05$), # – statistically significant difference compared to intact control ($p < 0.05$).

The very fact of monocyte migration into the regenerating liver can be considered as a positive effect of the spleen. Block of monocyte/macrophage migration into the liver after its resection leads to a slowdown of regenerative processes in it [19].

Thus, the accumulated data indicate both possible positive and negative effects of the spleen on reparative processes in the liver. What are such contradictions connected with? In our opinion, with the nature of those injuries, in which reparative processes in the liver and their interrelation with the spleen were studied. In those cases, when there is a pronounced death of hepatocytes, such as in hepatitis, liver fibrosis, the spleen becomes an additional source of synthesis of damaging cytokines, its removal stimulates reparative processes in the liver. In case of liver resection the level of cell death of hepatocytes is minimal [20], no products of their death enter the spleen through the systemic blood flow, and there is no excessive production of proinflammatory cytokines in the spleen. At the same time, if the spleen is removed under conditions of liver resection, it can lead to impaired migration of monocytes or any biologically active substances and, as a consequence, to impaired reparative processes. Probably, this partly explains the results of those works, in which the negative effect of splenectomy on the state of the liver in norm and regeneration after 70 % resection was shown [21–23].

Conclusion

Liver resection causes changes in the cytoarchitectonics of cell populations of the spleen. First of all, there is a decrease in the activity of proliferative processes in it, as well as changes in the state of the monocyte-macrophage system. A decrease in the content of CD115+ and F4/80+ cells in the spleen was found, which indirectly indicates the migration of monocytes/macrophages after liver resection.

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






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Состояние макрофагальной популяции и пролиферативная активность клеток селезенки в условиях регенерации печени

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Аннотация. *Актуальность.* В настоящее время все большее внимание исследователей привлекает участие клеток иммунной системы в регуляции репаративных процессов. Между печенью и селезенкой существует анатомическая связь посредством портальной вены. Таким образом, через портальную вену в печень из селезенки могут поступать цитокины и других биологически активных веществ, а также мигрировать клетки. Однако конкретные механизмы взаимного влияния указанных органов, в том числе при репаративных процессах, остаются мало изученными. Целью настоящей работы было изучить состояние моноцитарно-макрофагальной популяции селезенки после резекции печени, а также пролиферативная активность клеток селезенки при регенерации печени. Материалы и методы. В работе была воспроизведена модель регенерации печени после 70 % резекции у мыши. Животных выводили из эксперимента через 1 сут., 3 сут. и 7 сут. Иммуногистохимически выявляли маркер клеточной пролиферации Ki67, состояние моноцитарно-макрофагальной популяции селезенки оценивали по маркерам Ly6C, CD115, CD68, CD163, CD206 и F4/80 методами иммуногистохимии и проточной цитометрии. *Результаты и обсуждение.* Регенерация печени оказывала выраженной влияние на цитоархитектонику селезенки. Через 1 сутки после резекции печени в селезенке наблюдали снижение доли Ki67+клеток, по данным проточной цитометрии обнаружено уменьшение числа CD115+клеток, через 3 и 7 суток уменьшение числа F4/80+ макрофагов. *Выводы.* Резекция печени вызывает изменения и в состоянии клеточных популяций селезенки. В первую очередь, к снижению активности пролиферативных процессов в ней, а также к изменению состояния моноцитарно-макрофагальной системы. Установлено снижение содержания CD115+ и F4/80+клеток в селезенке, что косвенно свидетельствует о миграции моноцитов/макрофагов после резекции печени, что также может оказывать влияние на течение репаративных процессов в печени.

Ключевые слова: регенерация, печень, резекция, селезенка, макрофаги

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