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Effect of splenectomy on the course of reparative processes in the liver

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ABSTRACT

In mammals, the liver and spleen are closely related to each other and form the so-called liver-spleen axis. The functioning of this axis is based on anatomical connection through portal circulation, as well as the commonality of many functions performed. The connection between the liver and spleen is most pronounced in the development of such pathologic conditions as fibrosis and cirrhosis. Some clinical and experimental studies found that removal of the spleen leads to a decrease in the severity of liver fibrosis. A positive effect of spleen removal has also been found in liver resection and liver transplantation. Different authors suggest several mechanisms of this effect. It is assumed that the spleen in the development of fibrosis becomes an additional source of cytokines damaging the liver. In addition, monocytes and other leukocytes that support inflammation may migrate from the spleen to the liver. Another mechanism may be a decrease in blood pressure levels in the hepatic portal vein after splenectomy. Despite the available evidence, the mechanisms of this effect remain poorly understood. This issue is relevant for biomedical research, as it may form the basis for the development of new ways to treat liver diseases and stimulate its regeneration.

Keywords: liver; regeneration; repair; spleen; splenectomy; hepatic-splenic axis.

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Влияние спленэктомии на течение репаративных процессов в печени

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АННОТАЦИЯ

В организме млекопитающих печень и селезёнка тесно связаны друг с другом и формируют так называемую печёночно-селезёночную ось. В основе функционирования этой оси лежит анатомическая связь через портальную циркуляцию, а также общность многих выполняемых функций (утилизация чужеродных антигенов, продуктов распада гема и др.). Связь печени и селезёнки наиболее ярко проявляется при развитии таких патологических состояний, как фиброз и цирроз печени. В некоторых клинических и экспериментальных исследованиях обнаружено, что удаление селезёнки приводит к уменьшению выраженности фиброза печени, увеличивает приживаемость печёночных трансплантатов, а также уменьшает выраженность печёночной недостаточности после резекции печени. Авторы указывают на несколько механизмов такого влияния. Предполагается, что селезёнка при развитии фиброза становится дополнительным источником цитокинов, повреждающих печень. Кроме того, из селезёнки через селезёночную и далее — портальную вену в печень могут мигрировать моноциты и другие лейкоциты, поддерживающие воспаление. Другим механизмом может служить снижение уровня кровяного давления в портальной вене печени после спленэктомии. Несмотря на имеющиеся данные, механизмы такого эффекта остаются недостаточно изученными. Данный вопрос является актуальным для биомедицинских исследований, так как может лечь в основу разработки новых способов лечения заболеваний печени и стимуляции её регенерации.

Ключевые слова: печень; регенерация; репарация; селезёнка, спленэктомия; печёночно-селезёночная ось.

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脾切除术对肝脏修复过程的影响

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摘要
在哺乳动物机体中，肝脏和脾脏密切相关，形成所谓的肝脾轴心。该轴的功能基于通过门静脉循环的解剖学连接，以及许多功能的共性（利用外来抗原、血红素分解产物等）。肝脾之间的联系在肝纤维化和肝硬化等病理情况的发展中表现得最为明显。一些临床和实验研究发现，切除脾脏可降低肝纤维化的严重程度，提高肝移植的存活率，并减轻肝切除术后肝功能衰竭的严重程度。作者指出了这种影响的几种机制。据推测，脾脏在纤维化发展过程中会成为损害肝脏的细胞因子的额外来源。此外，支持炎症的单核细胞和其他白细胞可能会从脾脏通过脾脏和门静脉迁移到肝脏。另一个机制可能是脾切除术后肝门静脉的血压水平下降。尽管已有数据，但人们对这种效应的机制仍然知之甚少。这个问题与生物医学研究息息相关，因为它可能为开发治疗肝病和促进肝脏再生的新方法奠定基础。

关键词：肝脏；再生；修复；脾脏；脾切除术；肝脾轴。

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INTRODUCTION

The liver performs many functions, which determines its close connection with other organs. Such a relationship, in particular, is implemented between the liver and spleen and is interpreted as the hepatosplenic axis [1]. This interaction is based on the portal circulation (through the splenic vein). In addition, the liver and spleen are united by the commonality of the functions performed. This is, first of all, the binding of foreign antigens, as well as the products of hemoglobin destruction by macrophages.

Signs of a close relationship between the liver and spleen were first discovered by clinicians. It has long been known that liver pathology is accompanied by pathological changes in the spleen, such as splenomegaly and hypersplenism [2]. The hepatosplenic axis has been most extensively studied in the context of liver fibrosis, both in patients and in experimental models [3]. The main morphological manifestation of this disease is excessive proliferation of connective tissue in the liver. It was revealed that splenectomy causes a decrease in the severity of liver fibrosis.

Researchers suggest that the functioning of the hepatosplenic axis is based on the following mechanism: when the liver parenchyma is damaged (usually due to an infection or toxic effects) and hepatocytes die, then exosomes, chemokines, and molecular patterns associated with damage are released into the systemic bloodstream, reaching the spleen through the systemic bloodstream. Here, macrophages synthesize proinflammatory cytokines and growth factors that stimulate the synthesis of components of the intercellular substance. Cytokines, as well as lymphocytes and monocytes (and, possibly, other types of leukocytes) reach the liver through the portal circulation. This leads to the activation of the synthesis of the intercellular substance components, as well as the death of hepatocytes in other parts of the organ [4]. With splenectomy, the vicious circle is broken, so that molecular patterns associated with the injury still enter the systemic circulation but they do not activate the synthesis of cytokines or growth factors in the spleen. Thus, cytokines, as well as activated leukocytes, stop entering the liver through the portal vein, which decreases the level of damage to its parenchyma and synthesis of intercellular substance.

Despite the fact that the principle of the relationship between the liver and spleen in the hepatosplenic axis is generally understood by researchers, specific biochemical and cellular mechanisms remain poorly understood. We present scientifically substantiated mechanisms based on the literature data (Fig. 1). It is known that, depending on the factor that caused liver injury, there is specificity in the interaction of the liver and spleen; therefore, it is advisable to assess the role of the spleen in fibrosis, liver resection and its transplantation.

INTACT LIVER

Analysis of modern literature shows that there is very little information about the effect of splenectomy on the intact liver. It has been established that splenectomy leads to an increase in the mass of the intact liver of rats, and mitotically dividing cells are detected in it. It has been suggested that hepatocytes and resident macrophages enter the mitotic cycle [5]. In our work, it has been demonstrated using specific cellular immunohistochemical markers that mitotic figures are detected exclusively in hepatocytes. In addition, in experimental animals after splenectomy, the expression of the genes *IL-6* (interleukin-6), *IL-10, Tnf*-α (tumor necrosis factor α), *Hgf* (hepatocyte growth factor) and *Nos2* (nitric oxide synthase-2) increases in the intact liver, which probably leads to stimulation of hepatocyte proliferation [6]. It remains unclear what mechanisms cause changes in the expression of these genes in the intact liver. It can be assumed that splenectomy leads to changes in blood pressure in the portal vein [7], as well as to a decrease in the flow of hemoglobin

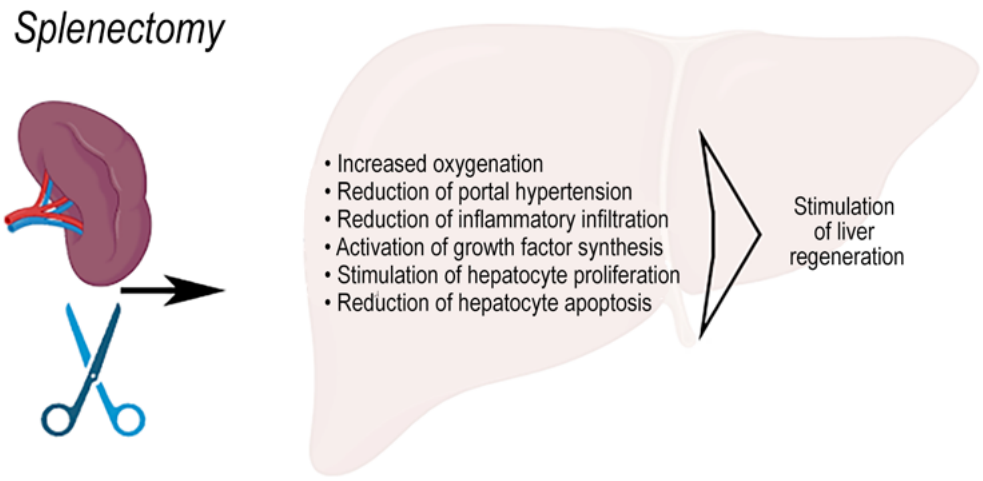

Fig. 1. Effect of splenectomy on liver regeneration.

utilization products into the liver [8]. These changes primarily affect the macrophage population, which we found indirect evidence for [6]. Activated macrophages synthesize a number of cytokines, including IL-6 and TNF-α, which activate hepatic stellate cells that synthesize HGF, the main mitogen for hepatocytes [9].

LIVER FIBROSIS

The mutual influence of the liver and spleen was first discovered in patients with liver fibrosis. The main source of synthesis of the intercellular substance components in the liver during the development of fibrosis are activated Ito cells which differentiate into myofibroblasts. TGF-β (transforming growth factor β) is currently believed to be the leading factor in the activation of Ito cells [10, 11]. Immunohistochemical studies in patients with liver cirrhosis revealed an increased content of TGF-β1 in the spleen and its colocalization with $CD68^+$ macrophages [12]. In this regard, the following mechanism is suggested. In patients with liver cirrhosis, the products of hepatocyte damage enter the spleen through the systemic bloodstream, where they activate red pulp macrophages. In turn, macrophages begin to synthesize TGF-β1, which enters the liver through the splenic and portal veins, where it activates Ito cells, as a result of which they begin to produce components of the intercellular substance. Splenectomy breaks this vicious circle and leads to an improvement in the liver structure [12]. Thus, splenic macrophages are an additional source of TGF-β synthesis. Directly in the liver, the products of hepatocyte death activate resident liver macrophages, which also stimulate the synthesis of TGF-β by Ito cells [10, 11].

One of the possible activators of fibrotic changes in organs is tumor necrosis factor receptor superfamily 14 (TNFSF14; also known as LIGHT). LIGHT is synthesized in many cells of the hematopoietic series, such as macrophages, eosinophils, and lymphocytes [13]. It has been established that LIGHT promotes disease progression in patients with pulmonary fibrosis, as well as collagen deposition in the dermis of the skin [13]. It was established in the study by Q.S. Liang et al. that LIGHT promotes the development of liver fibrosis by binding to LTβR (lymphotoxin-β receptor) and activating phosphorylation of JNK (Jun N-terminal kinase) [14]. This increases the secretion of TGF-β1 by macrophages, which results in liver fibrosis. It is noteworthy that the level of LIGHT in the blood serum of both experimental animals and patients decreased after splenectomy, which led to a decrease in the severity of liver fibrosis [14].

In addition to the secretion of cytokines into the portal bloodstream, leukocytes, including monocytes and lymphocytes, can migrate from the spleen to the liver. This phenomenon was revealed in a model of liver cirrhosis induced by long-term administration of CCl4 in mice. Splenectomy restored the balance of Th1/Th2 lymphocytes in the liver, which reduced the level of fibrosis [15]. In the study by H. Jiang et al., splenectomy reduced the level of liver infiltration by leukocytes, caused the release of TNF-α, cell apoptosis, and expression of caspase-3 [16]. In addition, in patients with hepatic cirrhosis after splenectomy, an increase in the counts of $CD8^+$ cells in the peripheral blood was registered, which caused a significant decrease in the $CD4^+/CD8^+$ cell ratio, slowing the progression of fibrosis and improving antitumor immunity [17]. In a study by A. Romano et al., which was focused on liver fibrosis associated with *Schistosoma japonicum*, it was established that splenomegaly correlates with a higher concentration of $FOXP3^+$ regulatory T cells in the blood and an increase in the severity of liver fibrosis. Splenectomy was accompanied by a decrease in the number of T cells and the severity of liver fibrosis [18]. Under conditions of infection with *Schistosoma japonicum*, the expression of chemokine genes, lymphocyte and monocyte cell adhesion molecules increased in the liver. In contrast, in the spleen, the expression of the corresponding genes decreased or did not change, which may indicate the recruitment of effector cells from the spleen to the liver [19].

Liver damage causes receptor-mediated activation of Kupffer cells, which is expressed in the synthesis and secretion of proinflammatory cytokines and chemokines by them, including CCL2. The chemokine CCL2 promotes the attraction of proinflammatory monocytes to the liver, which then rapidly differentiate into a local pool of monocyte-derived macrophages with a proinflammatory phenotype [20]. It has been revealed that splenic macrophages stimulate the secretion of CCL2 by liver macrophages, which results in monocyte migration and increased severity of liver fibrosis [21]. These studies are consistent with the work that established that the number of monocytes with the $CD11b^+CD43hiLy6Clow$ phenotype increases in the spleen of mice with liver fibrosis, which are recruited to the liver and differentiate into macrophages that stimulate the activation of Ito cells [22]. Other authors have demonstrated that splenectomy leads to the accumulation of monocytes/macrophages in the fibrotic liver, which is accompanied by a decrease in connective tissue neoplasm [23].

Thus, some authors postulate a weakening of leukocyte migration to the liver after splenectomy, while other researchers do not confirm this. Probably, one or another experimental or clinical model of liver cirrhosis plays a role in this process. In the experiment, a model of chronic administration of CCL4 is often used, and in the study where the accumulation of monocytes in the liver after splenectomy was demonstrated, thioacetamide was used to induce fibrosis [24].

Splenectomy also influences the effectiveness of the methods used to treat liver pathology. It was demonstrated in the study by T. Iwamoto et al. that splenectomy enhanced the repopulation of bone marrow cells in the liver affected by cirrhosis, which led to a decrease

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in collagen deposition in it. According to the authors, this effect is due to an increase in the expression of MMP9 (matrix metalloproteinase 9) in transplanted bone marrow cells [25]. In addition, it has been established that splenectomy increases the efficiency of transplantation of mesenchymal stem cells obtained from adipose tissue into the liver by increasing the expression of SDF-1 (stromal cell-derived factor-1) and HGF in the liver [26].

LIVER RESECTION

The effect of splenectomy on liver regeneration after resection was first studied in models of subtotal liver resection (removal of 80% or more of the mass) in rats. It has been established that splenectomy after such liver damage leads to increased stimulation of its regeneration. The probable causes of this phenomenon, as in liver cirrhosis, include the "resolution" of portal hypertension; a decrease in the degree of liver damage due to a decrease in the level of proinflammatory cytokines entering from the spleen; a decrease in vascular endothelial damage; inhibition of hepatocyte apoptosis [7, 27]. In particular, with 90% of liver resection, splenectomy leads to a decrease in the synthesis of acute phase markers in the remaining liver fragment, as well as to an increase in the synthesis of heme oxygenase-1, which improves reparation [28]. The flow of proinflammatory cytokines and the proliferation blocker TGF-β1 is terminated [29–31]. Due to this, the synthesis of HMOX1 (heme oxygenase 1) increases. HMOX1, in turn, suppresses the activity of TNF-α, which causes hepatocyte death. In addition, the synthesis of TGF-β1 and its receptor TGF-βRII decreases, and the synthesis of HGF and its receptor c-met increases [26, 29, 30, 32].

It is noteworthy that not only TGF-β1 has an inhibitory effect on hepatocyte proliferation after liver resection. IL-10 also has these properties. It has been established that after liver resection, the level of IL-10 synthesis increases both in the liver itself and in the spleen. Thus, splenectomy prevents the entry of IL-10 through the portal vein, which increases the rate of hepatocyte proliferation and positive dynamics of liver regeneration [33].

Other studies emphasized the role of oxygenation of the regenerating liver. It has been established that after splenectomy, oxygen delivery (HDO2) and its consumption (HVO2) by liver tissue structures increase in the resected liver of rats. Improved oxygen metabolism induced stimulation of hepatocyte proliferation [34, 35]. In addition, the results of the study [36] showed that the minimum residual liver weight required to restore its normal function decreased after splenectomy. Liver regeneration is known to require a huge amount of energy to meet increased metabolic needs [35, 37, 38]. Splenectomy increases significantly the oxygen supply, which is necessary for oxidative phosphorylation, which ensures liver regeneration [36]. This is probably due to a decrease in venous inflow and a relative increase in arterial blood flow [39]. In a study on a 70% liver resection model in mice, splenectomy accelerated regeneration by improving the formation of tight intercellular junctions, which contributed to the establishment of hepatocyte polarity through the Par 3-aPKC protein. In addition, splenectomy prevented paracellular leakage of bile components [40].

However, not all studies have demonstrated the positive effect of splenectomy on the condition of the damaged liver. A.G. Babaeva's work demonstrated the inhibitory effect of splenectomy on liver regeneration after its resection, and the strength of this effect did not depend on the time elapsed between liver resection and splenectomy [5]. The reason for this effect is unclear and requires further research. It is assumed that one of the reasons for the inhibition of regeneration after splenectomy may be a decrease in the level of proteinase inhibitors entering the liver. Thus, it was demonstrated in the study by A.V. Elchaninov et al. that with resection of 70% of the liver, an increase in the expression of genes encoding the synthesis of protease inhibitors (*Serpina3n, Stfa2*, and *Stfa2l1*) was noted in the spleen of mice [41]. The role of protease inhibitors in tissue regeneration has become the subject of experimental studies. In acetaminophen-induced liver injury, an increase in *Serpina3n* levels reduced the severity of necrotic and inflammatory changes in it [42]. A similar trend was noted in experimental ischemic stroke [43].

LIVER TRANSPLANTATION

The positive effect of splenectomy has also been demonstrated in the case of liver transplantation in patients with biliary atresia [44]. It has been established that simultaneous splenectomy improves the prognosis of liver graft survival and prevents the development of small-for-size remnant liver syndrome [45]. It has been revealed that splenectomy can lead to a decrease in portal hypertension, a decrease in the synthesis of proinflammatory cytokines and the level of cell apoptosis in the transplanted liver [46, 47]. The decrease in blood pressure in the portal vein is based on a decrease in the synthesis of endothelin-1, which is a key molecule in microcirculation disorders, since it causes narrowing of the liver sinusoids [48]. In the study by T. Matsuura et al., 15.8% of patients who underwent liver transplantation suffered from persistent thrombocytopenia and splenomegaly for seven years [49]. However, splenectomy resulted not only in regression of pancytopenia, but also in improvement of liver function [44]. Other studies also noted the key importance of portal vein pressure [50–52]. In contrast, C. Eipel et al. revealed that the beneficial effect of splenectomy in small liver lobe syndrome may be due to an increase in hepatic arterial blood flow with increased oxygen delivery, rather than a decrease in portal vein hyperperfusion into the liver remnant [39]. Improved oxygenation probably stimulates hepatocyte proliferation [34, 35].

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CONCLUSION

The spleen has a significant effect on the course of reparative processes in the liver. In most cases, this is demonstrated by splenectomy, which has a stimulating effect on the reparative processes in this organ. Depending on the nature of the liver damage, the effect of splenectomy is manifested through different mechanisms, namely a change in blood pressure in the portal vein, a decrease in the level of incoming cytokines and the number of leukocytes. However, not all studies have revealed a positive effect of splenectomy. The reasons for the contradictions are still unclear.

A positive or negative effect on the reparative processes in the liver probably depends on the nature of its damage. At the same time, the greatest number of studies have been performed on models of toxic liver damage. The effect of splenectomy on liver regeneration after resection has been studied much less. Based on the available literature, it is not possible to identify the main mechanism by which splenectomy affects the liver. The main attention of researchers should be aimed at studying the reaction of sinusoidal capillary endothelial cells, the liver macrophage population, as well as the process of leukocyte migration.

ADDITIONAL INFORMATION

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