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THE ROLE AND SIGNIFICANCE OF IMMUNE DISORDERS IN THE PATHOGENESIS OF ACUTE AND CHRONIC LIVER LESIONS

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Abstract: Recent immunological and immunomorphological studies over the past three decades have significantly transformed our understanding of the pathogenesis of both acute and chronic liver diseases. It has been established that immune dysfunction plays a central role in the progression of liver pathology to chronic forms, primarily through the development of autoimmune reactions and destructive inflammatory processes. In viral hepatitis types B and C, notable shifts in T- and B-cell immunity are observed, including T-helper deficiency, altered helper/suppressor ratios, and excessive antibody production. Circulating immune complexes (CICs) contribute to hepatocyte injury and microcirculatory disturbances. Experimental models such as heliotrine-induced and autoimmune hepatitis closely replicate the immunopathology seen in clinical cases, including lymphoid tissue atrophy and immune imbalance. Despite advances, the role of thymus-spleen interactions in the immune response to hepatic injury remains insufficiently explored. Understanding these mechanisms is crucial for the development of targeted diagnostics and immunomodulatory therapies for chronic liver diseases.

Keywords: Chronic hepatitis, immune disorders, T-lymphocytes, B-lymphocytes, autoimmune reactions, circulating immune complexes, spleen, thymus, liver cirrhosis, heliotrine model

Аннотация:Иммунологические и иммуноморфологические исследования последних трёх десятилетий существенно изменили представления о патогенезе острых и хронических заболеваний печени. Установлено, что иммунные нарушения играют ведущую роль в хронизации патологического процесса в печени, способствуя развитию аутоиммунных реакций и деструктивных воспалительных изменений. При вирусных гепатитах В и С наблюдаются выраженные изменения в Т- и В-звеньях иммунитета: дефицит Т-хелперов, нарушение соотношения хелперы/супрессоры, гиперпродукция антител. Циркулирующие иммунные комплексы (ЦИК) усугубляют повреждение гепатоцитов и микроциркуляторные расстройства. Экспериментальные модели гепатитов, такие как гелиотриновая и аутоиммунная, достоверно воспроизводят иммунопатологические процессы, выявляемые у пациентов, включая атрофию лимфоидной ткани и иммунный дисбаланс. Несмотря на достигнутый прогресс, роль взаимодействий между тимусом и селезёнкой при поражениях печени остаётся недостаточно изученной. Углублённое понимание этих механизмов имеет решающее значение для разработки новых диагностических и терапевтических подходов при хронических заболеваниях печени.

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Ключевые слова:Хронический гепатит, иммунные нарушения, Т-лимфоциты, В-лимфоциты, аутоиммунные реакции, циркулирующие иммунные комплексы, селезёнка, тимус, цирроз печени, гелиотриновая модель.

Immunological and immunomorphological studies conducted over the past three decades have significantly altered our understanding of the pathogenesis of both acute and chronic hepatitis [1,2,17,82,161,163,184,201,251,269]. It has been established that immune disorders in the body play a leading role in the transition of liver pathology to a chronic form, contributing to the development of autoimmune reactions and the progression of inflammatory-destructive changes in the liver [3,4,7,11,18,53,65,98,106,160,214,256].

Numerous studies on the immune status in hepatitis of various etiologies have revealed profound alterations in the T- and B-cell systems of immunity [10,12,44,49,69,83,97,187,273,275]. Immunological indicators have been, and continue to be, widely used in the differential diagnosis of various liver diseases [57,121,122,123,163,218,251,273].

A marked reduction in T-lymphocytes has been observed in severe forms and prolonged courses of acute viral hepatitis as well as in chronic hepatitis [11,18,49,53,100,171]. During remission or convalescence phases, both absolute and relative T-lymphocyte counts increased, although they did not reach normal baseline levels. The number of B-lymphocytes increased during the acute stage of the disease and especially during recovery; similar patterns were seen in prolonged cases of hepatitis B and C and in chronic active hepatitis [69,184,253].

The content of regulatory T-cell subpopulations varied widely across different forms of viral hepatitis B. According to several authors [12,17,40,49,84], T-helper levels decrease during acute phases. This deficiency increases as the disease becomes protracted, while the number of T-suppressors remains largely unchanged, even in severe forms of acute viral hepatitis B. In mild to moderate forms where a decrease in T-suppressors is observed, the hepatitis tends to progress into a prolonged course [163].

In cases where hepatic inflammation progresses to a chronic form, a significant decrease in T-suppressors is noted alongside a slight decline in T-helpers, especially evident in chronic active hepatitis. As a result, the helper/suppressor ratio initially suggests a deficiency of T-helpers but later indicates a predominance of T-suppressor deficiency [171,184]. Suppression of the suppressor function enhances killer activity, contributing to the aggressive progression of hepatocyte destruction [158,251].

Some authors have shown that immune deficiency in liver disease patients is not only due to reduced numbers of immunocompetent cells and altered subpopulation ratios but also to a significant impairment in their function [12,40,69,91,89].

Liver diseases, especially viral hepatitis B and C, are associated with disorders of both cellular and humoral immunity. These manifest as elevated globulin fractions in blood proteins, high antibody titers (including autoantibodies), and the presence of circulating immune complexes (CICs) [79,80,82,121,134,159,160].

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Some researchers attribute the increased antibody production in chronic active hepatitis to reduced activity of hepatic reticuloendothelial cells [17,18], while others consider it a manifestation of B-lymphocyte hyperactivity [20,21,74,76,253]. Alterations in immunoglobulin class content are also commonly observed in liver disease [83,122,163,184,218,273].

In chronic hepatitis, CICs play a crucial role in hepatocyte damage. These complexes can cause lysis of platelets and hepatocytes, releasing biologically active substances that increase blood clotting, disrupt microcirculation, and intensify hepatocellular hypoxia. Excess CICs also stimulate Kupffer cells and tissue macrophages to secrete enzymes and other biologically active compounds that further damage the liver [134,159,160].

The current concept of immune disturbances in chronic liver disease suggests that any damaging agent (virus, drugs, alcohol, toxins) disrupts hepatic cell membranes and releases lipoproteins that are part of specific hepatic antigens. These antigens trigger delayed-type hypersensitivity reactions in T-dependent lymphocytes, leading to lymphocyte-macrophage infiltration in the portal and intralobular regions. Sensitized immune lymphocytes then damage liver tissue. The release of new nonspecific hepatic antigens activates B-lymphocytes, driving humoral immunity. Over recent years, T-cell immune deficiency, particularly the imbalance of regulatory T-helper and T-suppressor cells, has been recognized as a central mechanism in chronic hepatitis [187,251].

The complexity of liver disease pathogenesis and the growing role of immune dysfunction necessitate adequate experimental models. Currently, the most widely used models of acute toxic and chronic hepatitis are those induced by heliotrine, carbon tetrachloride (CCl_4), thioacetamide, ethanol, or allyl alcohol, as well as autoimmune hepatitis induced by sensitization with hepatic autoantigens [1,2,8,9,26,28,55,68,74,76,110,115,120,214]. Heliotrine and autoimmune models closely resemble the structural and functional liver changes observed in clinical hepatitis B and C [2,214]. In these models, immune-mediated inflammatory destruction of the liver continues even after withdrawal of the hepatotropic agent and often ends in cirrhosis [2,80,90,91]. The autoimmune nature of heliotrine hepatitis is confirmed by high titers of autoantibodies against liver tissue [80].

Heliotrine hepatitis also exhibits immune disturbances similar to those in viral hepatitis B and C, including general lymphopenia, significant reductions in absolute and relative T-lymphocyte counts, and elevated relative levels of B-lymphocytes [67,140]. These quantitative shifts are accompanied by profound changes in the functional and metabolic parameters of lymphocytes [89,90,91].

Immunomorphological studies conducted at the Second Tashkent State Medical Institute revealed that experimental chronic heliotrine hepatitis (CHH) is marked by thymic cortical zone atrophy, reduced cell density in T-dependent zones of lymph nodes, Peyer's patches, and the spleen. Conversely, B-dependent zones showed increased proliferation of immunocompetent cells and high functional activity of subcellular organelles [7,65,106,127,128,133,269]. These changes are considered morphological correlates of the immune imbalance between T- and B-cell systems, resulting in autoimmune reactions [65,133,161,269].

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Immune abnormalities of various types were also identified in CCl_4-induced hepatitis [8,9,10,36,137,138]. Some studies demonstrated that CCl_4-induced toxic hepatitis produces both immunostimulatory and immunosuppressive factors [74,76], possibly derived from the spleen or the lysosomal destruction of hepatocytes. Reduced functional activity of lymphocytes was also noted in blast transformation and leukocyte migration inhibition assays. CCl_4 administration reduced T-lymphocytes in the spleen and blood, while B-lymphocyte numbers either increased or remained unchanged depending on dosage [8,9,10]. CCl_4 exposure suppresses helper and suppressor activity of immunocompetent cells [36]. Experimental evidence confirms the active role of mononuclear phagocytes, especially Kupffer cells, in the pathogenesis of experimental hepatitis [85,105].

In recent years, special attention has been given to autoimmune disorders in the pathogenesis of liver diseases and hypersplenism syndrome [46,50,56,64,163,184,232,234,256,275]. As early as the 1960s–70s, Tashkent researchers found high titers of autoantibodies against hepatocytes, erythrocytes, leukocytes, and platelets in patients with chronic hepatitis and cirrhosis. Similar findings were observed in animals with CHH and cirrhosis, where a strong correlation existed between autoantibody titers, liver damage severity, and hematological disturbances [41,79,80,90]. Later clinical-immunological studies confirmed that 64–85% of patients with chronic active hepatitis and cirrhosis complicated by hypersplenism had high levels of autoantibodies against erythrocytes, leukocytes, and platelets [17,25,46,116,185,186,213,218,232,239,252,270,271].

Splenectomy or exclusion of the spleen from portal circulation partially alleviates anemia and thrombocytopenia, but does not eliminate hypersplenism symptoms—likely due to persistent immune imbalance and ongoing autoimmune conflict.

These findings confirm that immune disorders play a pivotal role in the pathogenesis of liver diseases of various etiologies, particularly in hepatitis B and C, which frequently involve autoimmune mechanisms. Among toxic experimental hepatitis models, the heliotrine model most closely replicates chronic active hepatitis due to its autoimmune features. The involvement of immune mechanisms in chronic liver disease has been validated by numerous clinical and experimental studies [46,67,186,234]. Nevertheless, inter-organ immune relationships, particularly between the thymus and spleen under conditions of liver damage, remain poorly explored. The effects of a pathologically altered spleen on thymic structure and how splenectomy affects thymus function under normal and pathological conditions require further investigation.