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# THE SIGNIFICANCE OF CYTOKINES IN THE DEVELOPMENT OF LIVER FIBROSIS

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*The article analyzes the relationship of the cytokine system with the processes of fibrosis. It has been shown that the level of secretion of pro-inflammatory cytokines reflects not only the degree of liver dysfunction and the activity of the inflammatory process, but is also the main provoking factor in liver fibrosis. In the diagnosis of liver fibrosis/cirrhosis, cytokine status panels can be used. With liver fibrosis, there is a significant disruption in the synthesis of pro-inflammatory cytokines, which is manifested by an increase in the content of TNF-a, interleukin-2 and interleukin-6. The high level of proinflammatory cytokines in blood serum during liver fibrosis indicates their important role in the pathogenesis and progression of the pathological process.*

**Keywords**
*liver fibrosis, inflammation, cytokine, cirrhosis, pathogenesis*

Liver fibrosis (LF) is a key link in the development of a pathological process in the liver tissue, and the degree of fibrosis is a rather sensitive nonspecific marker of pathological changes in the liver under the influence of various etiological factors [1, 2]. Every year, more than 50 million people are infected with various types of hepatitis viruses, 1/10 of them have chronic viral hepatitis (CVH) and 1/5 cases of CVH end in cirrhosis, and 1/20 develop hepatocellular carcinoma [2].

According to some authors, there are currently approximately 60 million patients with liver cirrhosis (LC) in the world [3, 4, 5] and over the next 10-20 years, mortality may increase by 2 times [4, 5]. According to the latest WHO data published in 2017, deaths from liver diseases in Uzbekistan reached 7.936 or 4.7% of total mortality [6]. According to the authors, age-adjusted mortality is 32.38 per 100,000 population, Uzbekistan ranks 27th in the world [6].

According to a number of researchers, inflammation is a key pathogenetic factor in the development of cirrhosis [7]. Dirchwolf M., Ruf A. Dirchwolf M., Ruf A. (2015) described the syndrome of "cirrhosis-associated immune dysfunction", according to which the combination of immune dysfunction and systemic

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inflammation leads to the formation of fibrotic processes in the liver [9]. According to Zhou W.C., Zhang QB., Qiao L. (2014), damaged hepatocytes and endothelial cells are active sources of active oxygen radicals and fibrogenesis mediators, which activate macrophages, stellate cells and myofibroblasts, and the production of interleukins and interferons is enhanced [9].

As a result, the production of interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-23 (IL-23), and tumor necrosis factor alpha (TNF-α) is enhanced [10, 11, 12]. It should be said that cytokines are involved in the regulation of the development of the inflammatory response of the liver tissue, apoptosis and necrosis of liver cells, the development of cholestasis and fibrosis, but, paradoxically, these cytokines are simultaneously mediators of damaged tissue regeneration. There are different classifications of cytokines: a) pro-inflammatory (IL-1, IL-2, IL-6, IL-8, interferon-gamma (IFN-γ)); b) anti-inflammatory (IL-4, IL-10, transforming growth factor (TGF)); c) regulating cellular immunity (IL-1, IL-12, IFN-γ, TGF-β); d) regulating humoral immunity (IL-4, IL-5, IFN-γ, TGF-β). By the nature of the action, cytokines are: a) regulators of the immune system (IL-1, IL-18); b) antiviral cytokines (IFN-α, β, γ); c) cytokines with regulatory and toxic effects (TNF-α, TNF-β); d) chemokines; e) regulators of cell growth and differentiation (epidermal growth factor, fibroblast growth factor, TGF-β); f) regulators of reproduction of hematopoietic cells (colony-stimulating factors) [11]

Cells produce profibrotic and antifibrotic factors, their production is in dynamic balance. Fibrogenic cytokines include factors affecting proliferation and migration of stellate cells (platelet growth factor (PDGF)), basic fibroblast growth factor (FGF-2, FGF-b), insulin-like growth factors (IGF)); factors affecting the deposition of the extracellular matrix (TGF-β); factors that predominantly stimulate the contractility of stellate cells (in addition to proliferative effects) (endothelin 1, thrombin, angiotensin 2, vasopressin) [13, 14].

According to the authors, TGF-β appears to be key in the development of fibrogenesis. It stimulates the synthesis of extracellular matrix proteins and inhibits their degradation. Antifibrotic factors include metalloproteases (collagenase, gelatinase, stromolysin), their activity is suppressed by inhibitors of these enzymes, which are produced by the same cells [15]; antifibrogenic cytokines - IL-10, which is an antagonist of the main pro-inflammatory cytokine - TNF-α and suppresses the inflammatory process in the liver. At the same time, IL-1 and TNF-α, which activate the functions of Ito cells, are released in large amounts during liver damage [16, 17].

They produce thromboactivating factor (PDGF) and TGF-β1), which are involved in the pathogenesis and progression of liver damage (Fig. 1). Activated

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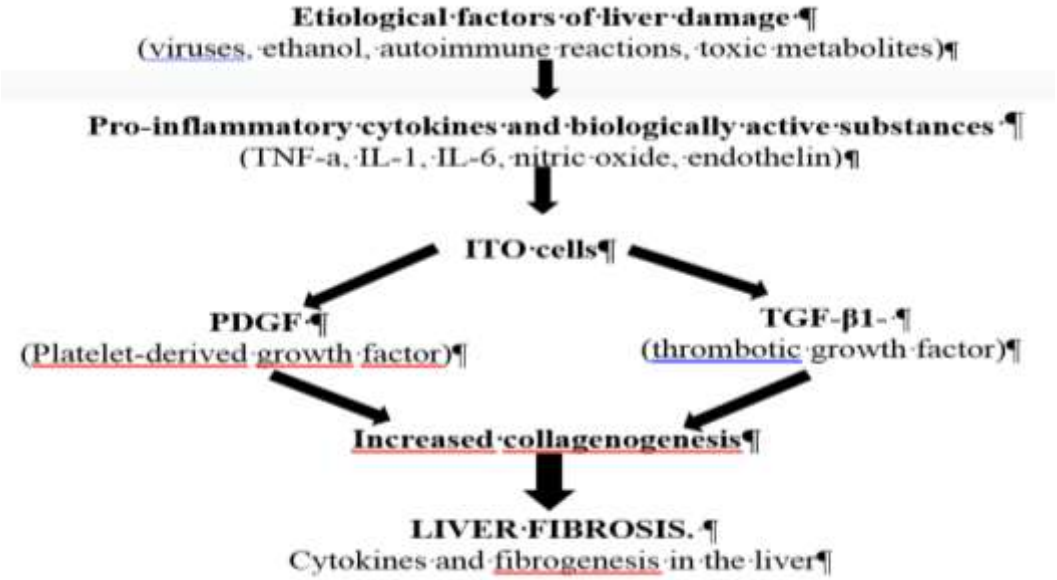
liver stellate cells proliferate, produce extracellular matrix components, predominantly type I and II interstitial collagen, basement membrane type IV collagen, as well as fibronectin, laminin, and proteoglycans [18, 19].




**Pic. 1. The role of cytokines in the mechanism of liver fibrosis [4]**

Thus, TNF-α plays a key role in the development of liver diseases. Data from clinical studies have shown that TNF-α mediates not only the early stages of metabolic disorders in the liver, but also the transition to a more advanced stage of liver fibrosis [10]. Activation of TNF-α and their receptors causes receptor aggregation, which leads to the formation of various adapter proteins that activate inactive kinases and proteases, including caspases. Mitochondria are also an important target for TNF-α-initiated signals leading to cell death [8, 14].

Sequential release from mitochondria of reactive oxygen species, cytochrome c and other factors that induce apoptosis ultimately contributes to the induced cell destruction. In the studies of Shapiro I.Ya., Sek O.O., Knoring B.E. (2002) showed that TNF-α is the first to be involved in the implementation of inflammatory and regenerative processes, which also enhances endothelial proliferation and collagen synthesis [20]

The authors established the relationship between the levels of TNF-a, IL-6 with the functional parameters of the liver and the characteristics of the course of cirrhosis. In other studies, it was found that an increase in TNF-a and its receptors in the blood serum of patients is associated with the activity of inflammation and the severity class according to the Child-Pugh scale [10]. According to the authors,

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hyperproduction of TNF-α is a sign of persistent systemic inflammation in cirrhosis and indicates the progression of the disease.

According to Dirchwolf M., Ruf A. (2015), cytokines such as IL-2, IL-6, IL-8 can be used as prognostic biomarkers, since they have a direct strong correlation and IFN-γ negative correlation with disease severity [ 8]. The authors showed that patients with cirrhosis in the stage of decompensation, characterized by the development of an excessive inflammatory response, are characterized by low values of IL-10, IL-12, TNF-a, macrophage chemoattractant protein-1 (MCP-1) and IFN-γ. The works of Zaman A. (2017) showed a significant increase in the level of IL-6 in the blood serum depending on the severity of the disease [21]. According to the author, the level of IL-6 in blood serum can serve as a marker for predicting progression and mortality in patients with cirrhosis. IL-6 has shown direct relationships with Child-Pugh stages of cirrhosis [22]. The levels of pro-inflammatory cytokines IL-6 and TNF-a correlate with functional liver tests (bilirubin content, transaminase activity), which confirms their ability to reflect the severity of hepatocyte damage. As the severity of liver damage increased, the concentration of granulocyte colony-stimulating factor is also increased [23].

The development of liver fibrosis/cirrhosis is associated with vascular remodeling, and regression of fibrosis may be accompanied by restoration of vascular changes [24, 25]. In this context, the possibility of using the definition as a test of differential diagnosis between fibrosis in chronic hepatitis and cirrhosis of the level of vasculoendothelial growth factor (VEGF), which stimulates neoangiogenesis and remodeling of the vascular system of the liver, is understandable. According to Shchekotova A.P. (2014) it is involved in the pathogenesis of chronic diffuse liver diseases, reflects endothelial dysfunction and stimulates liver fibrosis [26]. The concentration of this indicator depends on the degree of damage to the endothelium, which is triggered by a viral or other damage to hepatocytes, and makes it possible to diagnose cirrhosis with a sensitivity of up to 90% and a specificity of 78% at a cutoff point of 312 ng/ml[26]. Other markers of endothelial dysfunction can also stratify fibrosis and cirrhosis, as endothelial damage increases with the severity of liver damage. Endothelin and VEGF directly stimulate the production of coarse connective tissue by liver stellate cells [25]. A decrease in nitric oxide production and an increase in the synthesis of von Willebrand factor also progresses with the development of cirrhosis, including due to endogenous intoxication, so the more severe the liver damage, the more pronounced endothelial dysfunction. Markers of endothelial dysfunction can act as indirect tests of fibrosis in chronic diffuse liver diseases, especially since these

indicators have significant correlations with a direct marker of fibrosis, hyaluronic acid [26, 27].

The data obtained confirm the pathogenetic significance of inflammation in cirrhosis, which should be taken into account not only in the diagnosis and prognosis of this pathology, but also in monitoring and determining the tactics of treating patients. To clarify the significance of cytokines as indirect markers of liver fibrosis/cirrhosis, it is necessary to combine it with a biopsy or liver elastometry. In 2016, Perm scientists proposed a method for diagnosing the stage of AF with the inclusion of the pro-inflammatory cytokine TNF-α and albumin concentration in patients with chronic hepatitis C. The diagnostic model included platelet count, TNF-α level, and albumin concentration [23].

Thus, in the development of liver fibrosis/cirrhosis, cytokines are of great importance, which reflect the pathogenetic mechanisms of liver damage. Since chronic diffuse liver diseases are initiated or maintained by inflammation processes, the study of pro-inflammatory and anti-inflammatory cytokines deserves interest in this regard.

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