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ROLE OF CYTOKINES IN THE DEVELOPMENT OF LIVER CIRRHOSIS, WHICH DEVELOPED AS A RESULT OF CHRONIC VIRAL HEPATITIS D (REVIEW ARTICLE)

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ABSTRACT

Hepatitis D is an inflammation of the liver caused by the hepatitis D virus (HDV), which requires HBV for its replication. Hepatitis D infection cannot occur in the absence of hepatitis B virus. HDV-HBV co-infection is considered the most severe form of chronic viral hepatitis due to more rapid progression towards hepatocellular carcinoma and liver-related death.

Key words: viral hepatitis D, epidemiology, spread, treatment.

INTRODUCTION

Under conditions of inefficient SGD elimination, phenotypic activated lymphocytes that change in the course of infection chronicling form cytokines with profibrosis effects, which then trigger fibroblasts, endothelial cells, stellacites, as well as cause the marrow-derived recirculating cells to transform into myofibroblasts as well as the development of liver fibrosis. Cytokines are soluble proteins that are developed by a wide range of cells, primarily Th1 and Th2 type cells. These lymphocytes are able to recognize cells damaged by the virus and directly and indirectly control the strength of the immunological and inflammatory

response. In chronic viral hepatitis, the formation of cytokines and their levels are described as impaired due to the persistence of viruses [2].

Indeed, it has been established that the mechanisms of T-cell response are often incapable of controlling viral replication. In fact, it is the lack of T-cells that can lead to the persistence of viral infection, accompanied by a decrease in proliferative abilities as well as a violation of the formation of cytokines.

To a large extent, SD4+ Th2 immune response – related cytokines have been shown to create conditions for liver cirrhosis outbreak (IL -4, IL -5, IL -13, IL -21), at which time Th1 - related cytokines-Ifnu and IL -12 have anti-fibrosis properties.

The spectrum of lymphocytes forming cytokines against profibrosis and fibrosis is not limited to T-cells. Thus, it has been shown that previously activated star-like cells in the liver are influential in the thinning of ifnu-associated cell proliferation, which produces natural killers. In many studies, it has been noted that cellular ECT si leads to fibrogenesis in the liver through the development of profibrosis cytokines such as IL -4, IL -13, osteopontin. However, ECT can also reduce hepatic fibrosis under certain conditions through the development of Ifnu by means of curing star-like cells. At the same time, the potential of EC and ECT as target-cells is being discussed when conducting therapy against fibrosis[5].

Referring to the property of cytokines that trigger fibrosis changes in the liver, then Tfrß1 is characterized by a separately expressed profibrosis effect (transformative growth factor), which affects transcription of genes that respond to Receptor-Mediated I-III procolagene synthesis in myofibroblast membranes. In turn, with tfrß1 macrophages, IL -13 is effectively induced and controlled with Fnoa. A very important function of blocking fibrosis changes in the liver is performed by IL -10, the effect of which is indicated in a large number of models, including SGD [7].

Tfrß1 is the chief profibrosis cytokine that controls the formation and accumulation of extratellular matrix proteins, which is the strongest profibrosis stimulus for star – shaped cells. High expression of Tfrß1-beta is found in the pathogenesis of various diseases. In the absence of inflammation, Tfrß1 is secreted by adipocytes and kupfer cells, not by the hepatocytes themselves. Nevertheless, during the development of inflammation and liver damage, hepatocytes can become the main source of Tfrß1. Hepatocytes secrete Tfrß11 which can activate star-shaped cells in the liver. Biofaol Tfrß1 is needed to induce first – type collagen as well as smooth muscle actin α-starry hepatocyte activation and proliferation markers. SSG infection has been described as being associated with a significant increase in tfrß11 expression and its hepatic tissue and serum secretion. In addition, it can be said that many other viruses can also enhance the development

of Tfrß11, while in some cases Tfrß1 has a positive effect on viral replication. This cytokine, in addition, plays an important role in SSG/HIV convection, since in HIV-infection its participation increases SSG replication. [17,20]

In a study of the molecular mechanism of tfrß1 gene expression in response to SGD-infection, it was shown that tfrß1 gene expression is involved in AR1 Sr1, NFkB, and STAT-3 transcription factors, while the described effects of Tfrß1 are mediated by SMAD-proteins.

In liver fibrogenesis in patients with chronic liver diseases, the Tfrß1 effect also depends on the etymology of liver damage. For example, Tfrß1 and its Messenger Smad2 show a correlation with high levels of fibrosis in patients with chronic hepatitis v, alcohol steatogepatitis and noalkogol steatogepatitis rather than chronic SGD-infection. In patients infected with Schistosoma, Tfrß1 shows a negative correlation with fibrosis stages [18].

In addition to Tfrß1, an important profibrosis in various organs, including the liver, is tsitokin IL -13. IL -13 1 calls for expression of collagen as well as other important genes associated with fibrosis, such as tfrß1-associated α-smooth muscle actin (SMA) in star-shaped cells. It has been confirmed that a lack of IL -13 in mice led to decreased fibrosis. In addition, mechanisms that control the activity of this cytokine were studied, in which various negative control pathways were identified. It is a high affine receptor for IL-13ro2 – IL -13, as well as a key element of IL-12p40 – Th1-response [20].

The development of an effective immune response to infection, while limiting tissue damage, manifests itself in a delicate balance between inflammatory and anti-inflammatory effects. The immune response to pathogens involves the rapid activation of inflammatory cytokines, in which excessive inflammation can lead to an increase in systemic metabolic and hemodynamic disorders that are dangerous for the body itself. As a result of this, the immune system is simultaneously involved in inflammatory mechanisms, as well as the process of limiting tissue from damage, which is aimed at supporting and maintaining tissue gopeostasis [6,7].

Thus IL -10 is an anti-inflammatory cytokine and is necessary to control the immune response. Tsitokin, in principle, Th2 will be developed and in monocytes and macrophages, Class II thin out the expression of the head complex of histomuviousness. IL -10 limits the development of inflammatory cytokines (IL -1, IL -2, IL -6, IFNU), in addition, this cytokine can limit T-cell activation and differentiation, which subsequently leads to an inflammatory response in tissues. The lack of IL -10 formation can increase the inflammatory response to the entry of the microorganism as well as lead to inflammatory diseases in the internal

organs and some autoimmune diseases, including chronic inflammatory bowel diseases, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, spreading sclerosis, transplant rejection reaction, cancer. In other words, a decrease in IL-10 expression or a weakening of its signaling pathway has two distinct effects [27,30].

Originally IL -10 was defined as Th2-associated cytokine, however, development of IL -10 has been shown to be associated not only with T-cell population, but also with all leukocytes. The source of IL-10 In vivo is T-helpers, monocytes, macrophages, and dendritic cells. In this case, a huge variety of immunocomponent cells, including V cells, cytotoxic T cells, EC, mastocytes, granulocytes (neutrophils and eosinophils), are added to the formation of IL -10 in certain cases. In addition, nonimmune effector cells can also be involved in the development of IL -10: these are epithelial cells and keratinocytes involved in the formation of IL -10 in response to infectious invasion, tissue damage, as well as tumor growth.

It is known that this cytokinin indirectly affects effector cells by altering immune functions by preventing the maturation of macrophages and dendritic cells as well as limiting their ability to costimulate, antigen presentation, and chemokine development, suppressing fibrosis-associated and V-cell proliferation as well as life expectancy, producing T-helices that control the development of cytokinins such as Fnoa, Ifnu, and IL -12. Disruption of IL -10 signaling pathways is in contrast associated with increased adaptive immune response, including the formation of FNOA CD4+ T - cells and other inflammatory cytokines [17].

The immunosuppressive activity of IL -10 is mediated by its heterodimer receptor (IL-10r1, IL-10r2). Despite the fact that the IL -10 receptor complex is expressed to many cells in various variants, monocytes and macrophages are first-class targets for this cytokine. Receptor coupling activates the JAK/STAT signaling pathway, leading to major changes in the expression character of immunomodulatory genes. This effect serves to thin out the inflammatory effects of mediators, reducing antigenprezentation and phagocytosis, in addition to increasing the inhibitory functions of monocytes and macrophages, which create conditions for a decrease in their effectiveness and the implementation of their cleansing function [9].

In addition, IL -10 can directly or indirectly suppress cell development, quench Cellular and allergic response, and enhance the control functions of T-lymphocytes either directly, or by acting on anti-inflammatory molecules such as IL-1 receptor antagonist (il-IRA), soluble receptor Fnoa, and IL -27. IL -10 can enhance activation and proliferation of specific immune cells, including

mastocytes, SD8+ and T-cells, EC and V-cells, but the consequences of such activity have not been studied so far.

It is also worth saying that some pathogens can use Il -10's immunosuppressor abilities to infect the pathogen as well as provide positive cases for persistency with Il -10 homologs, which bind to compatible receptors and call for an immunological response similar to that in the endogenous ligand-bound state. This is typical for the Epstein-Barr virus, for example. Thus, it is likely that the physiological role of IL -10 during infectious diseases consists in limiting the tissue lesions that the negative and excessive effects of inflammation call. Nevertheless, the effect of IL-10 formation can lead to the development of a state of decompensation at the time of severe infection and disrupt the effectiveness of the work of the immune system and lead to the persistence of infection or fulminant course of the disease [9,20].

It is worth saying that in the case of many infections, in particular Leismania donovani, Ersinia pestis, Ersinia enterosolitisa, IL -10 is an important marker of a poor prognosis of the disease. On top of that, some pathogens have mechanisms that allow IL-10 to be controlled during the development of infection, possibly to ensure favorable microinvasion.

It is also interesting to consider the mechanisms that allow persisticity in an organism with HIV, SGD herpesvirus. In these cases, an increase in IL -10 levels can be observed, which leads to impaired antigenprezentative cell differentiation and thus leads to a decrease in the effectiveness of antigen presentation and calls for T-cell-dependent suppression of the antiviral response. For this reason, with an immune-controlling effect, it was found that non-human levels of IL -10 Can Release pathogens from immune system control for extended periods of time, allowing the pathogen to persistently develop. Proof of this concept is the chronic viral inflammatory model using LCMV clone. In this model, the systematic derivation of IL -10 is consistent with a lack of tstl response. [20]

By a team of researchers, who do not report a response reaction to IFN therapy, SGD patients show a decrease in disease activity in long therapy with IL -10. This data is based on normative levels of ALT, inflammatory changes in the liver as well as decreased fibrosis. But, unfortunately, treatment in this way leads to an increase in viral replication.

When IL-10 levels were studied in 49 patients with untreated SGD, no major difference in this cytokine level was detected between patients and the control group. In this, a relationship was noted between the levels IL -10 and AST. Despite the fact that the level of transaminase has changed during chronic SGD infection, the increase in these enzymes, especially ast, is very likely to be considered a

reliable marker of necroaryngeal activity. Thus, it can be confidently noted that high levels of IL -10 in patients with SGD reflect the level of inflammatory destruction [27,29].

Also, in the field associated with the development of IL -10, the detection of a heterozygous variant can lead to the outbreak of viral hepatitis in the white population and it has been described that Quechua is associated with a higher risk of chronicling. For this reason, there are grounds that the damage of the immune system associated with genetic predisposition or induction with certain viral proteins TX1 and tx2 call for predominant activation of cells, followed by the formation of immune-controlling cytokines, as well as an imbalance between the suppression of T-cell reactions [17].

All the information provided confirms the large role of cytokines in the mechanisms of development of fibrosis changes in the liver of patients with chronic hepatitis V and C and provides the basis for attempts to use the described phenomena in the development of new methods of treatment of these diseases. These attempts are based on the assumption that liver fibrosis can be reversible and inhibited either by means of thinning and proliferating star cell activation or by controlling different cells in methods related to cytokine in the immune system.

In particular, the most likely factors of reverse management of liver fibrosis are Ifnu-forming EC cells. In Vivo EC cell activation or treatment using Ifnu has positively influenced fibrosis processes called with carbontetrachloride in the liver, according to some authors. In addition, clinical studies have shown that Ifnu therapy weakens liver fibrosis in some patients with SGD infection. However, in other clinical studies, it has been noted that Ifnu therapy does not have a positive effect in the form of weakening the severity of fibrosis and cirrhosis prevalent in patients with chronic SGD infection [19].

The reasons for such contradictory results to each other are not known. One explanation may be the selection of different patients with different expressions of liver disease. It has been shown in studies evaluating the effectiveness of the action of Ifnu+ EC on liver fibrosis in early and advanced stages of liver fibrosis in Vivo, as well as in various stages of liver star cell activation in vitro. At the beginning of the process or in its early stages, the action of Ifnu has been shown to prevent liver fibrosis in rodents by increasing Ifnu+ EC activity and suppressing the function of Star cells. On the other hand, the antifibrotic effects of Ifnu decreased in widespread fibrosis through tfrß1 and SOCS1 protein induction, as well as activation of the primary mediator of the STAT-1 – Ifnu signal. This data allowed the authors to predict that Tfrß1 and retinoid acid lead to impaired function of EC cells and Ifnu signaling pathways, with only expressed hepatic fibrosis [20].

This assumption is also supported by the fact that neutralizing antibodies block Tfrß1 by increasing EC-cell killing and maintaining Ifnu formation in EC. In addition Tfrß1 is known as an EK-associated cytotoxicity and cytokine-forming inhibitor. Summing up all that has been written, it can be concluded that Tfrß1 plays an important role in quenching the effect of Ek cell antifibrosis as well as the stagnation of interactivated star cells to EK killin, that the established ways of using Ifnu in therapy require large developments.

Another direction in controlling the fibrosis process in the liver is due to the fact that nuclear factor-dependent kappa V (Nfkb) thymusstromal lymphoprotein (TSLP) development occurs when hepatocytes become infected. TSLP tx17 from hepatocytes-induces dendritic cell differentiation into money activating a powerful source of cytokines with an inflammatory effect. Infected hepatocytes are able to activate monositar-derived dendritic cells by controlling secreting TSLP CD40, CD86, CCL17, CCL22, CCL20 expression, which are markers of dendritic cell activation. In addition, the formation of major cytokines, IL -6 and IL -21, for Th17-Tfrß beta differentiation increases in SGD-infected cell cultures due to monocytes. It is interesting that the blocking of TSLP using neutralizing antibodies prevents dendritic cell activation as well as subsequent development, as well as the formation of cytokines that affect the differentiation of T-helices towards tx1. Thus, the blockage of TSLP carried out by SGD-infected hepatocytes can quench the induction and development of Thl7-jaw in the liver and stop the progression of chronic diseases in the liver to fibrosis and liver failure [30].

In patients with SGD, there is another direction in the management of tsitokin status, which has not been practically described to date – this is the participation of serotonin.

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