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On the Mechanism of the Immune-Mediated Pathway of Apoptosis in the Formation of Fibrotic Changes in the Liver and the Development of Methods for Pharmacological Correction (Experimental Study)

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Correspondence of the recommended dissertation topic with the main directions of scientific and technical research of the republic. This study was carried out in accordance with the priority direction of the development of science and technology of the republic VI "Medicine and pharmacology", and within the framework of SSTP-9 "Development of new technologies for the prevention, diagnosis, treatment and rehabilitation of human diseases."

The importance of the problem. Liver fibrosis (LF) is the main link in the development of a pathological process in the liver tissue, and the degree of fibrosis is a quite sensitive nonspecific indicator of pathological changes in the liver under the influence of various etiological factors [Didenko V.I., 2013; Maleev V.V., 2016 and etc]. According to WHO forecasts, over the next 10-20 years, mortality from liver diseases will increase by 2 times [Lebedeva E.I. 2019]. Every year, more than 50 million people become infected with hepatitis viruses, approximately 10% of those who have been ill develop chronic viral hepatitis (CVH), in 20% of cases, CVH ends with cirrhosis, and 5% develop hepatocellular carcinoma. According to a number of authors, there are currently approximately 200 million patients with chronic liver diseases in the world, about 30% of them are cirrhosis of the liver (LC) [Bazarny V.V. 2018]. According to the latest WHO data published in 2017, deaths from liver disease in Uzbekistan reached 7,936 or 4.7% of total mortality [Uzbekistan Health Profile, WORLD HEALTH ORGANIZATION 2017]. According to the authors, the age-adjusted mortality rate is 32.38 per 100,000 population, Uzbekistan ranks 27th in the world.

The reason of this is that the liver is not only an organ in which the central links of the metabolism of proteins, lipids and carbohydrates take place, but also a barrier to all unfamiliar substances that enter the human body [S.V.Okovity 2012]. Structural and functional changes in hepatocytes, slowing down of synthetic processes in them, violation of metabolic processes leads to a decrease in the detoxification function of the liver, the accumulation of endo- and exobiotics in biological media, the development of endotoxemia cause the development of multiple organ failure, further aggravating the course of the underlying disease [E.F. Agletdinov, A.A. Nikonorov, F.Kh. Kamilov, 2009]. In this regard, the problem of studying the molecular mechanisms of chronic liver damage, its transition to cirrhosis under the influence of toxic agents remains an important area of modern experimental and clinical hepatology [S.A. Belyakin, A.N. Bobrov, S.V. Plusnin, 2011].

Three types of cell death are known: necrosis, apoptosis, and terminal differentiation. Apoptosis provides physiological balance and genetic stability of the organism due to self-destruction of genetically modified, defective cells. Apoptosis is a genetically regulated process that requires energy storage and the synthesis of certain proteins. The result of apoptosis is the gradual and slow disposal of cells that are no longer functionally needed. Activation of the nuclear factor (NF-kB) increases the expression of adhesive molecules (E-selectin, VCAM-1, ICAM-1) stimulating the transendothelial migration of leukocytes. Activated NF-kB serves as one of the important regulators of inflammatory genes, increasing the synthesis of cytokines and inducible enzymes (cyclooxygenase-2, collagenase, NO-synthase).

In this regard, the problem of drug correction of liver damage with herbal preparations is extremely crucial. Wide application of hepatoprotectors, choleretic agents, and metabolic drugs with versatile effects has been found. The study of the mechanism of their hepatoprotective action will allow not only to expand the arsenal of effective domestic hepatoprotectors, but also to introduce them into clinical practice.

The degree of knowledge of the problem. The central link in the pathogenesis of toxic liver damage is oxidative stress, hypoxia, dysfunction of oxidase and oxygenase enzyme systems, impaired calcium metabolism - a consequence of direct exposure to the toxin or its metabolite formed as a result of biotransformation. The direct cause of this deficiency in many pathological conditions is a decrease in oxygen supply, an imbalance of oxidative processes, activation of the immune-mediated and mitochondrial pathways of apoptosis, fibroblast growth factors, causing irreversible fibrosis processes, leading to chronicity of the pathological process. Damage and destruction of hepatocytes is the starting point in the activation of other cell populations, which, in turn, initiate an inflammatory reaction, an adaptive immune response with the development of reactive fibrosis (cirrhosis) of the liver and hepatocellular cancer (Ivashkin V.T. 2009).

Nowadays, for the treatment of toxic liver damage, herbal remedies are widely used [V.M. Pokrovsky, O.G. Kompaniets, 2008; L.V. Kravchenko, 2008; M.S. Nikolaev, 2012 and etc.]. Essential phospholipids are the most widely used among drugs with hepatoprotective properties. The mechanism of their protective action depends on with the restoration of hepatocyte cell membranes, their participation in the processes of molecular transport, cell division and differentiation, stimulation of the activity of various enzyme systems, antioxidant action, slowing down collagen synthesis and increasing collagenase activity, which underlies their antifibrotic effect [O.I. Kiselev 2006; N.I. Geivandova 2008; S.S. Sokolovskaya 2008; E.P. Yakovenko 2011; and etc.].

Thus, the analysis of literature data shows a trend towards an increase in various liver lesions. This problem is important in both medical and social fields. Despite the presence of hepatoprotectors with different mechanisms of action, their effectiveness remains low, which dictates the need to develop new highly effective hepatoprotectors and study their mechanism of action. All of the above is the subject of future research.

Purpose of the work: to study the mechanism of immune-mediated apoptosis in chronic liver damage and to develop methods for their correction.

To achieve this goal, the following tasks were formulated:

1. Determine the main parameters of the immune-mediated mechanism of apoptosis: nuclear factor NFkB, sAPO-1/FAS (sCD95), sFAS ligant (FASL).

2. Determine the activity of arginase 1 (ARG1, Liver Arginase), the correlation of its activity with the indicators of cytolysis, cholestasis, mesenchymal inflammation and hepatocellular insufficiency.
3. Establish the relationship between the above factors of apoptosis and the mechanisms of liver fibrosis.
4. Evaluate the effectiveness of new herbal preparations katacin and geranil in slowing down the processes of fibrosis.

Scientific novelty of the research.

For the first time on the model of chronic liver damage, the key factors of immune-mediated apoptosis and the mechanism of the hepatoprotective effect of the new domestic hepatoprotector on these indicators will be deciphered. Based on the data obtained, the effectiveness of the use of new domestic herbal preparations in hepatology will be substantiated.

The practical significance of the work.

The conducted experimental studies will allow not only elucidating the subtle molecular mechanisms of the immune-mediated mechanism of apoptosis in chronic liver damage, but also the effect of hepatoprotectors and submitting relevant documents to the Pharmacological Committee of the Republic of Uzbekistan to obtain permission for its use in clinical hepatology.

Material of research.

Experimental studies will be carried out on 120 mature male rats in order to accomplish the scheduled task. The model of chronic toxic liver injury will be reproduced by administering heliothrin at a dose of 2.5 mg/kg for 8 months 2 times a week. The object of the study will be katacin and geranil, and carsil will be used as a reference drug. Pharmacotherapy will be carried out after morphological confirmation of chronic liver damage. Studies will be conducted on the 40th, 50th and 60th day from the start of the experiment.

Research methods.

1. Biochemical indicators (fibro-test).
2. By determining the nuclear factor NFkB, sAPO-1/FAS (sCD95), sFAS ligant (FASL), the immune-mediated pathway of apoptosis will be studied.
3. The activity of arginase 1 (ARG1, Liver Arginase), general biochemical parameters of the liver will be determined.
4. Sectioning methods will be used for histochemical and morphometric confirmation of the mechanism of formation of liver fibrosis.
5. Statistical research methods with the calculation of mean values, standard error, Student's t-test, correlations, sensitivity, specificity and predictive value methods will be used.

Implementation of the obtained results.

Obtained results will be discussed and published in the materials of various international and regional conferences, symposiums, congresses; will be published in periodicals of near and far abroad countries, republican editions; methodological manuals, information letters will be issued. The results of the study will be introduced into the work of the hepatological departments of the clinics of the republic and into the educational process of the Department

of Medical and Biological Chemistry of the TMA.

Area of application: therapy, hepatology, pharmacology, fundamental medicine.