**ABSTRACT**

of the dissertation for the degree of Doctor of Philosophy (PhD) in 6D060700 Biology

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**LIVER STRUCTURE UNDER CONDITIONS OF PERIPHERAL TUMOR GROWTH AND CORRECTION BY LITHIUM CARBONATE**

**Urgency of the topic**: It is known that hepatocarcinoma (HC) is one of the most common, aggressive and drug-resistant tumors in humans. (Shen, Cao 2012). Liver is the most common organ of distant metastases in tumor growth with various localization. Liver cancer is one of the most aggressive tumors in humans, characterized by low survival rate. Liver has many functions, including detoxification, production of various hormones and proteins, storage of vitamins. It plays a key role in the regulation of blood sugar, production and secretion of bile, ketone bodies, and regulation of lipid metabolism. (Silantyeva, N.T., 2016). Furthermore, liver, as the central organ of detoxification and metabolism, is most susceptible to the toxic effects of malignant growth products. It is known that various lithium compounds (lithium chloride, lithium carbonate) can affect signaling pathways and cell cycle regulation. It was revealed that lithium acting by suppressing the activity of kinase-3β glycogen synthase can affect the development of apoptosis, the activity of vascular growth factor, chemotaxis of neutrophils, and contribute to an increase in circulating CD34 + hematopoietic stem cells. Also, lithium compounds are considered as potential agents of targeted therapy (Di Salvo D.N., 2012) capable of slowing tumor growth. There are no data in the literature on the effect of lithium on the liver structure when it is used as an antitumor drug. In connection with the steady increase in oncological morbidity, it is relevant to study structural changes in the liver as a result of tumor growth in distant organs, with the aim of correcting its condition to maintain homeostasis of the body.

 **The purpose and objectives of the study.** The aim of this research is to study the liver structure in conditions of distant tumor growth and the use of lithium carbonate as an antitumor drug.

 In accordance with the purpose of the study the following **objectives** were set:

1. To study the liver structure of CBA mice in normal conditions.

2. To study structural changes in the liver in the dynamics of peripheral tumor growth modeling.

3. To study the ultrastructure of hepatocytes in the dynamics of peripheral tumor growth.

4. To study structural changes in the liver and hepatocytes when using lithium carbonate per os.

5. To study structural changes in the liver and hepatocytes with the introduction of lithium carbonate along the periphery of tumor growth.

**Scientific novelty.** New data are presented for the first time on structural changes developing in the liver when modeling distant tumor growth - hepatocarcinoma-29 in the thigh muscle tissue in experimental animals. It was established that under conditions of distant tumor growth, there are structural changes that develop in the liver: a decrease in the volume and numerical density of hepatocytes, an increase in the volume density of sinusoid spaces, an increase in the size of liver prelimphatics – Disse's spaces, swelling of sinusoidal endothelial cells, an increase in the gaps of the lymphatic vessels of the portal tracts. The observed structural changes in various parts of the lymphatic drainage of the liver under conditions of distant tumor growth indicate an increase in the processes of lymph formation associated with the presence of toxic metabolites in the blood.

It was observed that structural signs develop by the 30th day of tumor development in hepatocytes, indicating a violation of the protein-synthetic and energy function of cells. There is a decrease in the volume density of the hepatocyte cytoplasm, the volume density of the cisterns of the granular endoplasmic reticulum, mitochondria and the numerical density of attached and free polysomal ribosomes. The results obtained indicate a developing insufficiency of the secretory function of the liver in conditions of peripheral tumor growth.

 An increase in the volume density of lysosomal structures in the dynamics of tumor growth was established for the first time. Electron microscopy revealed all stages of intracellular autophagic degradation: the presence of autophagosomes, autophagolysosomes and secondary lysosomes in the cytoplasm of hepatocytes. Fragments of cytoplasm, glycogen rosettes, mitochondria, fragments of the endoplasmic reticulum with ribosomes were found in autophagosomes. The data obtained indicate that non-selective autophagy develops to maintain intracellular hepatocyte homeostasis, as well as energy and trophic homeostasis of the body in conditions of distant tumor growth in the liver.

It was found that with the introduction of lithium carbonate along the periphery of tumor growth and the oral administration of lithium carbonate, there is an increase in the volume density of mitochondria, glycogen, cisterns of the granular endoplasmic reticulum, numerical densities of attached and free polysomal ribosomes, which indicates the correction of the protein-synthetic and energy function of hepatocytes.

 **Key points for thesis defense and conclusions:**

1.In conditions of distant tumor growth in the liver, there is a decrease in the volume fraction of parenchyma cells and an increase in the stromal component of the organ, indicating an increase in lymphopoiesis.

2. In conditions of distant tumor growth in hepatocytes, there is a development of structural signs of impaired protein-synthetic, energy function of cells, which reflect the developing insufficiency of the secretory function of the liver.

3. When modeling peripheral tumor growth in hepatocytes, the process of non-selective autophagy develops to maintain intracellular hepatocyte homeostasis, as well as energy and trophic homeostasis of the body.

4. The oral administration of lithium carbonate and the administration of lithium carbonate along the periphery of tumor growth have a corrective effect on the structure of the liver and the ultrastructure of hepatocytes.

**Theoretical and practical relevance.**

The results of the study contribute to fundamental lymphology, cell biology and morphology, and may have applied and practical significance.

It has been established that under conditions of distant tumor growth, the following structural changes develop in the liver: dysfunction of the protein-synthetic and energy functions of cells, an increase in the processes of lymphopoiesis in the organ, insufficiency of the secretory function of the liver. The oral administration of lithium carbonate and the administration of lithium carbonate along the periphery of tumor growth have a corrective effect on the structure of the liver and the ultrastructure of hepatocytes.

The results found practical application in the laboratory of physiology of the project system of Research Institute of Clinical and Experimental Lymphology, a branch of the Institute of Cytology and Genetics of Siberian Branch of the Russian Academy of Sciences in Novosibirsk (Russia), in the laboratory of physiology of the lymphological system of the Institute of Human and Animal Physiology of the Science Committee of the Ministry of Education and Science of the Republic of Kazakhstan in Almaty (Kazakhstan), and it was introduced into the curriculum of S. Toraighyrov Pavlodar State University in the course “Cell Biology” for students of the major “5B060700 Biology”.

The main provisions of the thesis are included in the course of lectures for students of S. Toraighyrov PSU, Pavlodar.

**Practical evaluation of the work.** The main research results were presented and discussed at international scientific conferences: international conference “Problems of studying the conservation of biodiversity and biological resources and their use”, Almaty (Kazakhstan), 2016; International morphological scientific and practical competition-conference of students and young scientists “Morphological sciences - the fundamental basis of practical medicine”, dedicated to the memory of Professor M.Ya. Subbotina, Novosibirsk (Russia), 2016; III International scientific and practical conference “Fundamental scientific research: theoretical and practical aspects”, Kuzbass (Russia), 2017; II International morphological scientific and practical competition-conference of students and young scientists “Morphological sciences - the fundamental basis of medicine”, dedicated to the memory of Professor M. A. Samoteikina, Novosibirsk (Russia), 2017; International scientific and practical conference “IX Toraigyrov readings”, Pavlodar (Kazakhstan), 2017; International conference on lymphology, Bishkek (Kyrgyzstan), 2018; XIII International scientific and practical conference “Lymphology: from basic research to medical technology”, Novosibirsk (Russia), 2018; International scientific and practical conference “Actual problems of ecology and nature management of Pavlodar region”, Pavlodar (Kazakhstan), 2018.

The relationship of this work with other scientific and research works and various state and international programs. This work was supported by a grant from JSC Center for International Programs, Agreement No. 4141 dated December 26, 2016 (Kazakhstan), and budget funding from the Research Institute of Clinical and Experimental Lymphology, a branch of the Institute of Cytology and Genetics of Siberian Branch of the Russian Academy of Sciences, No. 0324-2019-045-S-02.

**Publications:** 14 works were published on the topic of the dissertation, including 4 articles in journals recommended by Education Oversight Committee of the Ministry of Education and Science of RK, 2 articles in an international scientific publication having a non-zero impact factor on the Scopus information database, 8 articles in materials of international conferences.

**The structure and scope of work on the topic**. The dissertation consists of introduction, three chapters, findings, conclusion, list of references. The total volume of the manuscript is 116 pages, including 18 tables and 30 figures. The list of references includes 293 sources and annexes.