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Morphological Features of Liver Regeneration Processes in Experimentally Induced Cirrhosis

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ABSTRACT

We studied the dynamics of hepatocyte proliferation after liver cirrhosis in rats, assessed the ratio of cell proliferation and cell death processes against the background of transforming growth factor β (TGF-β). Morphological changes in the liver in experimental cirrhosis were studied to assess the degree of fibrotic changes, the nature of hepatocyte damage and the state of the microcirculatory bed, the effect of TGF-β on regenerative processes in the liver by analyzing its effect on hepatocyte proliferation, activation of stellate cells and changes in the structure of the liver parenchyma.

KEYWORDS: liver, morphology, rats, cirrhosis, regeneration, experiment.

Objective. To study the dynamics of hepatocyte proliferation after liver cirrhosis in rats, to evaluate the ratio of cell proliferation and cell death processes.

Materials and research methods. The work was performed using experimental animals: Wistar rats. The experiment was conducted on laboratory male Wistar rats weighing 200–250 g, which were induced to develop liver cirrhosis in order to model chronic liver damage. All experimental animals were kept in a vivarium equipped in accordance with the requirements of the "Sanitary Rules for the Arrangement, Equipment and Maintenance of Experimental Biological Clinics (Vivariums)" No. 1045-73. Animals were slaughtered using inhalation anesthesia with fluorothane vapor. In the experimental series (n=30), after opening the abdominal cavity, the liver was isolated without damaging it. Excision of biopsy material was performed 3, 7, 30 days after the experiment. Paraffin blocks and sections 5-7 μm thick were prepared, stained with heme-eosin, Van Gieson and Masson. The required areas were photographed. To reproduce the experimental cirrhosis, a classical model of toxic liver damage was used by repeated administration of ethanol in rats. When modeling liver cirrhosis, ethanol was used in experimental studies to study alcoholic liver disease. The effectiveness depended on the dose, duration and route of ethanol administration. Oral administration was performed through a gastric tube, preferably for a more accurate dosage. The accepted dosing scheme: 5-7 g / kg body weight / day (20-30% ethanol solution) in drinking water. A concentration of 20-30% provides a high degree of consumption without giving up liquid. This is equivalent to severe chronic alcohol intoxication in humans. Alternative scheme: 4-5 g/kg body weight/day by gavage. Used for more controlled ethanol

consumption. Induction duration ranges from 1 to 3 months. At 8-12 weeks - initial stages of fibrosis and steatosis. At 16-24 weeks - pronounced morphological changes in the liver characteristic of cirrhosis (pseudolobes, necrosis, inflammation) against the background of ethanol intake. The control group received distilled water. Animals' condition was assessed by monitoring body weight, behavior, and blood biochemistry.

Results of the study and their discussion. During the study of liver regeneration in cirrhosis modeling, pronounced morphological changes characterized by the staging of recovery processes were revealed. At the early stages (3-7 days), activation of cell proliferation was observed, mainly in the peripheral zones of the liver lobules. In these areas, an increase in the number of hepatocytes with signs of hypertrophy, as well as increased expression of nuclear markers of mitotic activity were noted. Against the background of activation of regenerative processes, accumulation of fibrous structures in the portal tracts and perisinusoidal spaces was revealed. One of the key mediators of fibrogenesis is TGF-β1, which is present both intracellularly and in the extracellular matrix. Analysis of the dynamics of changes in the number of TGF-β1+ cells revealed statistically significant differences between the experimental and control groups throughout the observation period (χ^2=48.3; $p<0.01$). By the seventh day, a reliable decrease in the number of TGF-β1+ cells was noted in both groups ($p<0.05$), although the differences between them remained insignificant ($p>0.1$). On the 30th day, the number of TGF-β1+ cells in both groups leveled off, being within 0–3 cells ($p>0.74.5$), which indicates the similarity of their dynamics at this stage of recovery.

CONCLUSIONS. Morphological changes in the liver in experimental cirrhosis were studied in order to assess the degree of fibrotic changes, the nature of hepatocyte damage and the state of the microcirculatory bed. The effect of TGF-β on regenerative processes in the liver was determined by analyzing its effect on hepatocyte proliferation, activation of stellate cells and changes in the structure of the liver parenchyma. The obtained data confirm that liver regeneration in cirrhosis is accompanied by complex interrelated processes of hepatocyte proliferation, fibrogenesis and extracellular matrix remodeling, in which the dynamics of TGF-β1 expression plays a key role.

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