

Abstract

Objective: Cholestasis-induced liver injury is known to be one of the major factors contributing to the development of hepatic pathologies. Ligation of the common bile duct induces proliferation of epithelial cells and cholangiocytes, as well as activation of portal fibroblasts and hepatic myofibroblasts. These processes promote inflammation, formation of fibrotic scar tissue, and ultimately the development of liver fibrosis and cirrhosis. At the same time, under cholestatic conditions, the liver exhibits adaptive responses to increased functional load. One such process is hepatocyte polyploidization, which is manifested by an increase in the number of high ploidy cells. It's known that during cholestasis, JNK1/2 and p38 are activated in hepatocytes; However, their role in the initiation of the polyploidization process has not been fully elucidated. The aim of the present study was to determine whether the JNK1/2 and p38 signaling pathways participate in the initiation of polyploidization as an adaptive response in the cholestatic liver.

Materials and Methods: Experiments were carried out on adult white rats using a cholestatic liver model induced by common bile duct ligation (CBDL). Experiment was performed by using JNK1/2 inhibitor - SP600125 and P38 inhibitor - SB203580. Proliferative activity was evaluated using the colchicine mitotic index, while alterations in hepatocyte ploidy were analyzed using Feulgen staining and ImageJ software.

Results: Inhibition of JNK1/2 didn't alter neither hepatocyte mitotic activity nor the quantitative distribution of polyploid hepatocytes, indicating that JNK1/2 isn't involved in the initiation of polyploidization at the early stage of cholestasis. In contrast, inhibition of p38 significantly reduced the high ploidy hepatocytes induced by CBDL without affecting mitotic activity.

Conclusion: Based on the obtained results, we can conclude that under conditions of increased functional load caused by CBDL, at the initial stage of cholestatic liver, the increase number of high ploidy cells is achieved through the activation of p38 MAPK cascade.

Keywords: JNK1/2 and P38 signaling pathway, Cholestatic liver, Polyploidization