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# Critical Role of Hypoxia-Mediated TGF-beta and Metabotropic Glutamate Receptor2/3 during the Fibrotic and Cirrhotic Condition in Rat Liver

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Many studies have reported that TGF-β1 is being increased in cirrhosis. And then, how is the expression of TGF-β1 increased in cirrhotic liver without the increase of MFBs, chief producing cell of TGF-β1? We examined the expression of TGF-β1, phosphorylated-Smad2/3 (p-Smad2/3) of the TGF-immediate down stream signaling system and hypoxic status during hepatic fibrogenesis induced by carbon tetrachloride. TGF-β1 was mainly produced by hypoxic hepatocytes at cirrhosis although myofibroblasts and macrophages producing TGF-β1 were decreased. Moreover, distribution of p-Smad2/3 in hepatocytes was consistent with those of hypoxic hepatocytes regardless of myofibroblasts. TGF-β1 expression in hepatocytes might have been associated with hypoxia. Based on proteomic analysis, upregulated protein spots focused in this study perfectly matched masses identified by mass spectrometry. Eleven spots on 2-D gels derived from fibrotic liver perfectly matched masses identified by mass spectrometry and identified. Among these proteins, four proteins well corresponded to calcium/calmodulin-dependent protein kinase 1, metabotropic glutamate receptor 2/3, oxidoreductase Erp57, thioredoxin peroxidase 1 at 14 week. The most highly induced protein, metabotropic glutamate receptor 2/3, was approximately 10-fold over-expressed compared with that of other two groups. In immunohistochemistry, there are no positive cells for mGluR2/3 at week 0. However, a number of macrophages expressing mGluR2/3 were mainly detected in the fibrous septa at week 14. We put forward the hypothesis that TGF-β1 is mainly produced by myofibroblasts and macrophages at early and middle stages of fibrotic processes, but it is predominantly released by hypoxic hepatocytes in the last fibrotic stage or cirrhosis. In addition, the upregulation of mGluR2/3 during the process of fibrosis and cirrhosis may critical role for processing of hepatic fibrosis and cirrhosis, which leads to hepatic carcinoma.

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