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Regulation of Pathological Markers during Hepatic Fibrogenesis in Rats

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Introduction

Hepatic fibrosis is a common response to various chronic hepatic injuries and occurs as a consequence of the transformation of hepatic stellate cells into myofibroblasts (MFBs) producing abnormal extracellular matrix which is mainly induced by transforming growth factor-beta (TGF-β), especially TGF-β1 [1,2]. As the liver becomes fibrotic, there are both quantitative and qualitative changes in several pathological markers related to the hepatic fibrosis. These fibrotic markers in liver are mainly consisted of several proteins and cytokines, but sometimes included specific type cells. The aim of this study was to detect expression and change of markers (TGF-β, mallory body, cytokeratin, α-SMA, hypoxia, collagen) during hepatic fibrogenesis.

Materials and Methods

Hepatic fibrosis was induced by CCl_4 on Male Wistar rats for 14 weeks. We divided rats into two groups. Group 1 (n=32) was cirrhotic group with CCl_4 treatment for 14 weeks and four rats were sacrificed at 0, 2, 4, 6, 8, 10, 12 and 14 week respectively. Group 2 (n=4) is recovery group with CCl_4 treatment for 12 weeks and was allowed to recover during 2 weeks. In this study, we used several techniques with HE, Azna, IHC, Immunoblot and Proteomics.

Results

Mallory body(MB) and oval cells were detected during hepatic fibrosis. In IHC, MB-like inclusions and oval cells were positive for CK8 and CK18. Expression of TGF-β1 was mainly detected by hypoxic hepatocytes at cirrhosis although myofibroblasts(MFBs) and macrophages producing TGF-β1 were decreased. Moreover, distributions of p-Smad2/3 in hepatocytes were consistent with those of hypoxic hepatocytes regardless of MFBs. Furthermore, in recovery, most MFBs disappeared in liver, whereas positive reactions of p-Smad2/3 still existed in the hepatocytes of hypoxic areas. Spots of glutamic receptor and heat shock protein were detected in cirrhotic and recovery groups, respectively.

Discussion

we demonstrated that TGF-β1 was mainly produced by hypoxic hepatocytes at cirrhosis although MFBs and macrophages producing TGF-β1 were decreased [3]. Moreover, distributions of p-Smad2/3 in hepatocytes were consistent with those of hypoxic hepatocytes regardless of MFBs. Furthermore, in recovery, most MFBs disappeared in liver, whereas positive reactions of p-Smad2/3 still existed in the hepatocytes of hypoxic areas. Therefore, TGF-β1 expression in hepatocytes might have been associated with hypoxia. Based on present knowledge, we put forward to hypothesis that TGF-β1 is mainly produced by MFBs and macrophages at early and middle stages of fibrotic processes, but it is predominantly released by hypoxic hepatocytes when last fibrotic stage or cirrhosis occurred. We also present the formation of MBs and collagen fibers in rat hepatocytes with CCl_4-induced hepatic fibrosis. This represents the first CCl_4 experimental in vivo model of MB induction which will be useful for further investigations on the mode of formation and progression of MBs and their role in the pathogenesis of cell damage. Furthermore, this model provides an opportunity to study the production of collagen fibers on hepatocyte, and etiology and pathogenesis of oval cells simultaneously.

References

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