

Editorial

Can serum cytokines predict hepatic cytokine expression in liver cirrhosis?

Cytokines are involved in liver injury and cirrhosis. However, studies to explore whether systemic and hepatic cytokine levels can help in predicting cirrhosis progression are limited. Common bile duct ligation (BDL) is a well-established animal model used to induce cholestatic liver injury with inflammation, fibrosis, and cirrhosis.¹ The study by Hsieh et al study is characterized by a systemic approach to evaluate the overall picture of hepatic and circulating cytokines, including IFN- γ , TNF- α , IL-10 and TGF- β , during cirrhosis development.² Their study shows that cirrhosis development is associated with progressively enhanced hepatic pro- and anti-inflammatory cytokine expression in BDL rats. However, corresponding serum concentrations were not completely in accordance with hepatic cytokine expression in BDL rats.² Hsieh et al conclude that circulating cytokine concentrations may not totally reflect their hepatic expression levels during the development of cirrhosis.²

The roles of cytokines, which may be responsible for initiation and progression of hepatic injury, fibrosis and cirrhosis, but can also participate in liver regeneration, are complicated in hepatic damage.³ Elevated circulating TNF- α has been observed in patients with alcoholic liver disease, especially those who are malnourished, and has been correlated with survival.⁴ Increased circulating TNF- α has been reported in patients with viral hepatitis.⁵ Hepatic expression of TNF- α is upregulated in autoimmune liver disease, alcoholic hepatitis and cirrhosis.⁶ Hsieh et al observed that hepatic TNF- α expression rather than serum TNF- α was markedly elevated in BDL rats.² A previous study suggested that TNF- α plays a central role in hepatic regeneration following both toxic and partial hepatectomy. Exogenous TNF- α stimulates hepatic DNA synthesis in rodents and accelerates recovery of liver weight following partial hepatectomy.⁷ Hepatic regeneration following chemically induced hepatotoxicity is also impaired in TNF type 1 receptor knockout mice and following anti-TNF- α antibody administration.⁷ In fact, Kupffer cell blockade augments hepatic regeneration following partial hepatectomy secondary to impaired IL-10 release from these cells, which allowed sustained unopposed TNF- α production from endothelial cells.⁸ Hsieh et al observed that the trends for serum TNF- α changes were not consistent with those for hepatic TNF- α expression levels, which suggests that measurement of serum TNF- α cannot reflect hepatic TNF- α expression.²

Previous studies revealed that hepatic IFN- γ mRNA correlated with the degree of liver damage.⁹ Natgonat et al reported

that hepatic IFN- γ mRNA expression was higher in liver biopsy specimens from patients with primary biliary cirrhosis than in normal control individuals.¹⁰ The study by Hsieh et al is the first to directly measure hepatic IFN- γ expression by immunohistochemical staining.² Consistent with a previous study, Hsieh et al find that serum concentrations of IFN- γ were not in parallel with hepatic expression levels during progression of hepatic inflammation and necrosis.^{2,11} It has been reported that hepatic levels of TGF- β were positively correlated with the degree of liver fibrosis in rats with biliary cirrhosis.¹² Hsieh et al show that serum TGF- β concentrations are positively correlated with hepatic TGF- β expression in BDL rats. In patients with primary biliary cirrhosis, high serum TNF- α is accompanied by severe liver fibrosis, as graded by liver biopsy. Meanwhile, regression of hepatic fibrosis on ursodeoxycholic acid therapy is associated with decreases in serum TNF- α in patients with primary biliary cirrhosis.¹³ Taken together, these interesting results indicate that serum TNF- α might be a candidate marker for prediction of the degree of liver fibrosis.

The endogenous anti-inflammatory cytokine IL-10 has potent anti-inflammatory and anti-fibrotic properties. In carbon tetrachloride-induced liver injury, IL-10 inhibits acute inflammation and limits the proliferative response of hepatocytes and delays the development of fibrosis during liver repair.¹⁴ Hsieh et al observed that higher hepatic IL-10 expression was accompanied by lower serum levels of IL-10 in BDL rats than in sham rats. The mechanism for relatively low serum IL-10 might involve rapid clearance of IL-10 by BDL-induced cirrhotic liver due to upregulation of the hepatic IL-10 receptor.¹⁵

In conclusion, the study results reported by Hsieh et al are valuable in furthering our understanding of progressive enhancement of both pro- and anti-inflammatory cytokine expression in liver during the development of cirrhosis in BDL rats.² Nonetheless, only some of the changes in serum cytokine concentrations are consistent with the corresponding hepatic expression, which implies that a complex interplay of cytokine production, utilization and metabolism occurs in liver injury.

Ying-Ying Yang

*Division of General Medicine, Department of Medicine,
Taipei Veterans General Hospital, Taipei, Taiwan, ROC*

E-mail address: yangyy@vghtpe.gov.tw

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