Pleiotropic effects of CD5L in hepatic inflammation and fibrosis

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Chronic hepatic inflammation leads to liver cirrhosis, which is currently the 11th most common cause of death worldwide. Numerous pathologic processes including viral infections, alcoholic abuse, nonalcoholic steatohepatitis (NASH), and autoimmune diseases are characterized by chronic liver damage and inflammation. It is well known that pathogen-associated molecular patterns (PAMPs) trigger immune responses leading to the activation of hepatic stellate cells (HSCs) and liver fibrosis, which eventually progress to cirrhosis and liver cancer [1]. Identifying the underlying mechanism of inflammation and fibrosis is crucial for the development of novel treatment paradigms for chronic liver diseases.

CD5-like protein (CD5L) is a soluble glycoprotein that circulates in blood. The previous paper by Aran et al. sheds light on the pathogenesis of liver cancer by studying the involvement of CD5L. Overexpression of CD5L in hepatocytes, macrophages and serum enhances liver cancer cell colony formation and proliferation, which was associated with poor outcome in hepatocellular carcinoma (HCC) patients [2]. However, the impact of dysregulated CD5L signaling on early stage hepatic inflammation and fibrosis is poorly understood.

In an article of EBioMedicine, Bárcena and colleagues explored the role of CD5L in hepatic inflammation and fibrosis with human samples from hepatitis and cirrhotic patients and the widely used rodent model of CCl4-induced fibrosis [3]. The authors demonstrated that serum levels of CD5L significantly increased and correlated to the stage of liver fibrosis, suggesting that serum CD5L is strongly associated with liver disease severity. By immunohistochemistry in liver tissues, a correspondence has been identified between circulating CD5L and its hepatic protein expression levels. This finding as well as other recent studies have provided new insight for the detection of advanced fibrosis in clinical practice using non-invasive blood-based diagnostic tests [4,5].

Carbon tetrachloride (CCl_4) is the most routinely used hepatotoxin to study liver fibrosis and cirrhosis in rodents [6]. CCl_4 mice develop a phenotype resembling human liver cirrhosis with the induction of hepatic inflammation, which promote HSC activation and liver fibrosis. The authors noted that the expression of CD5L was significantly increased in not only total liver, but specific hepatic cell populations (hepatocytes and macrophages) as well. However, other cell types in the liver, such as HSCs, neutrophils and T cells, showed very low levels of CD5L. It is important to note that treatment with rCD5L markedly reduced hepatic injury and liver fibrosis induced by CCl_4 treatment. Interestingly, this study highlights the involvement of recruited immune cell populations. It was found that rCD5L treatment significantly decreased neutrophil infiltration along with phenotypic shift in monocytes from $Ly6C^{hi}$ (pro-inflammatory) to $Ly6C^{low}$ (anti-inflammatory). Thereby, the recruitment of inflammatory components to the liver may be mediated by CD5L in CCl_4-induced fibrosis.

The transforming growth factor β1 (TGFβ1) signaling pathway plays important role in liver fibrosis. It contributes to the activation of HSCs and results in excessive production of extracellular matrix (ECM), including collagen type I. SMAD proteins have been studied extensively as downstream transcription factors of TGFβ1. During the activation of HSCs, phosphorylation of SMAD 2/3 is profibrotic, whereas SMAD7 negatively mediates SMAD2/3-induced fibrogenesis [7,8]. In this original article, the authors evaluated the expression of CD5L in cultured human hepatic stellate cell lines (hHSCs and LX2). Consistent with the low CD5L level in isolated HSCs from mouse liver, there was almost undetectable CD5L expression in cultured HSCs. In addition, treatment of rCD5L did not trigger the activation of hHSCs and LX2. Interestingly, it was found that rCD5L significantly decreased TGFβ-induced expression of pro-fibrogenic factors in cultured HSCs, including TGFβ, Col1a1, α-SMA and VEGF, via activation of SMAD7 and inhibition of SMAD2/3 nuclear translocation, suggesting that the CD5L axis may be an important novel target to limit fibrosis.

Early studies suggested that CD5L exerted differential functions depending on the types of target cells and its combined effects with other cytokines [9]. Besides the antiapoptotic role of CD5L in macrophages and hepatocytes in the setting of liver cancer, it has been reported that CD5L also regulates Th17 cell differentiation by modulating lipid metabolisms [10]. Bárcena and colleagues discovered HSCs as a novel cellular target of CD5L, suggesting that CD5L may have pleiotropic effects in liver fibrosis. Future work should identify the contribution of CD5L in cell-to-cell crosstalks between HSCs and hepatocytes, and/or HSCs and macrophages. Additionally, it will be important to further evaluate the role of CD5L in liver fibrosis in other well studied rodent models, such as bile duct ligated (BDL) mice, Mdr2-deficient mice and other models of cirrhosis. The results of these experiment would greatly strengthen the findings linking CD5L with hepatic inflammation and liver fibrosis. Since different stages of liver fibrosis may be regulated by specific cell types and signaling mechanisms, understanding these differences in relationship to CD5L may be beneficial for personalized treatment.

Overall, the manuscript by Bárcena et al. is the first to reveal the functional involvement of CD5L in ameliorating hepatic inflammation, HSC activation and downstream liver fibrosis. The findings described in this study have the potential to provide new evidence that can be explored for the development of novel diagnostic markers for fibrosis and therapeutic target to treat chronic liver diseases.

References

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