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Fibroblast growth factor inducible 14 as potential target in patients with alcoholic hepatitis

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Alcoholic hepatitis is a distinct clinical entity characterized by jaundice and liver failure that generally occurs after decades of heavy alcohol use. Recovery from alcoholic hepatitis is determined by abstinence from alcohol, the presence of mild clinical symptoms and the implementation of appropriate therapy. Unfortunately, patients with severe alcoholic hepatitis have a high mortality rate of about 40% to 50% despite optimal medical management [1]. A significant percentage of patients succumb to bacterial infections with infection-attributed mortality of 12% to 54% [2] underscoring the importance of bacterial translocation and an impaired immune response. Moreover, patients with alcoholic hepatitis have a profound often sepsis-like hyper-inflammatory state suggesting the possibility that proinflammatory mediators such as cytokines contribute to alcoholic hepatitis by promoting systemic inflammation and systemic inflammatory response syndrome (SIRS).

Tumor necrosis factor (TNF)- α has been proposed to be the critical cytokine involved in the pathogenesis of alcoholic hepatitis mostly based on animal models of experimental alcoholic liver disease [3]. Inhibition of TNF α attenuates alcoholic liver injury in rats [4]. Elevated plasma TNF α is a significant predictor of decreased long-term survival in patients with severe alcoholic hepatitis [5]. However, clinical trials using an anti-TNF α strategy resulted in disappointing outcomes [6, 7]. In patients with moderate to severe alcoholic hepatitis, etanercept was associated with significantly higher rates of serious infections and higher mortality rate after 6 months [7]. Therefore, new targets for treatment of patients with severe alcoholic hepatitis are needed.

In the current study, Affo et al. assessed the hepatic transcriptome in patients with alcoholic hepatitis and compared this to normal liver and other chronic liver diseases such as chronic hepatitis C infection and NASH. Surprisingly, ligands such as TNF α and FAS were not differently expressed in livers with alcoholic hepatitis, while TNF superfamily receptors TNF-related apoptosis-inducing ligand (TRAIL)-R1 and Fibroblast growth factor inducible 14 (Fn14) were markedly overexpressed. Patients with higher Fn14 gene expression had worst 90-day survival and showed more severe portal hypertension than patients with lower hepatic gene expression. Fn14 was expressed mainly in hepatocytes and in particular in a subpopulation of progenitor cells in patients with alcoholic hepatitis. Hepatic gene

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expression of Fn14 in experimental mouse models was increased following liver injury induced by various etiologies. The largest fold increases were observed after acute ethanol or acetaminophen exposure and to a lesser extent in a model of acute ethanol administration on chronic carbon tetrachloride injections model mimicking alcoholic hepatitis. These results from animals raise the question whether ethanol alone induces hepatic Fn14 gene expression. Because the study is lacking a human control group with alcoholic liver disease (without evidence of alcoholic hepatitis), future studies need to investigate Fn14 expression in various stages of alcoholic liver disease. The exclusive overexpression of Fn14 in alcoholic hepatitis, but not in normal liver or liver samples from patients with NASH, chronic HCV infection, is a completely novel finding. However, Fn14 protein expression is upregulated in cirrhotic liver secondary to NASH cirrhosis or alcohol abuse [8].

Interestingly, hepatic gene expression of TNF-like weak inducer of apoptosis (TWEAK), a ligand for Fn14, was unchanged, while serum levels were significantly less in patients with alcoholic hepatitis as compared to healthy controls. The TWEAK/Fn14 pathway appears to promote pathogenesis in disease target tissues through Fn14 upregulated on parenchymal cells [9]. On the other hand, there is evidence that Fn14 regulation is sufficient for its biological function independent of TWEAK as shown for differentiation of myoblasts into myotubes [10].

The question arises how increased Fn14 expression might contribute to the pathogenesis of alcoholic hepatitis. TWEAK stimulates oval cell proliferation in mouse liver through its receptor Fn14 [8]. The authors have shown by staining techniques that Fn14 colocalizes with markers of liver progenitor cells in liver specimens from patients with alcoholic hepatitis. Interestingly, it has been suggested that TWEAK/FN14 may induce the expansion of progenitor cells during acute liver injury to promote tissue regeneration, while persistent TEWAK/Fn14 signaling inhibits progenitor cell differentiation [9]. Thus, the induction of Fn14 following acute alcohol intoxication might be helpful for liver regeneration, while a continuous activation might be deleterious, resulting in impaired liver regeneration and contributing to disease progression in alcoholic hepatitis. And indeed, the authors suggested in a previous publication that liver regeneration might be impaired in patients with alcoholic hepatitis [11].

Fn14 might promote alcoholic hepatitis not only by affecting progenitor cell proliferation and differentiation, but also by affecting other disease-driving processes. Several studies support this notion. In a murine choline-deficient, ethionine-supplemented (CDE) model of chronic liver injury, Fn14 knockout mice showed significantly reduced liver progenitor cell numbers, attenuated inflammation and fibrogenesis [12]. Systemic delivery of an adenovirus encoding TWEAK but not an adenoviral control vector induced fibrosis in mouse heart, liver, and kidneys [9]. The importance of Fn14 in the pathogenesis of kidney ischemia reperfusion injury has been demonstrated by Fn14 blockade using an anti-Fn14 blocking monoclonal antibody, which downregulated the local expression of several proinflammatory mediators and reduced accumulation of neutrophils and macrophages in ischemic tissues. Most importantly, it attenuated the development of chronic fibrosis after ischemia reperfusion injury and significantly prolonged the survival of lethally injured mice [13]. It is therefore possible that in addition to its effect on progenitor cells, Fn14 might promote

proinflammatory processes in a pathological state such as alcoholic hepatitis and might exert a direct profibrogenic effect on hepatic stellate cells. Further cell specific studies are required to delineate the exact mechanism of action.

Obviously, whether Fn14 is a surrogate marker for severe cases of alcoholic hepatitis or whether it is truly involved in the pathogenesis requires additional studies using preclinical mouse models with genetically manipulated mice or using neutralizing antibodies. However, this will be a challenging experiment as no experimental animal model of alcoholic hepatitis has been established. The authors approach this challenge by using a novel acute-on-chronic mouse model, in which chronic liver injury is induced by repeated injections of carbon tetrachloride followed by a single dose of ethanol by gavage. Fn14 is still significantly induced in this model, but to a lesser extent as compared to acute ethanol gavage.

Understanding the exact mechanisms by which alcohol results in alcoholic hepatitis will greatly enhance our ability to design preventive and therapeutic interventions. This approach may lead to a novel therapy for patients with alcoholic hepatitis, which would inhibit disease progression and reduce mortality without affecting the systemic immune system. Thus, targeting the Fn14 pathway may be a promising new target for alcoholic hepatitis.

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