Integrin alphavbeta6 is a marker of the progression of biliary and portal liver fibrosis and a novel target for antifibrotic therapies.

BACKGROUND/AIMS: The integrin alphavbeta6 promotes proliferation of specialized epithelia and acts as a receptor for the activation of latent TGFbeta1. We studied alphavbeta6 expression in experimental and human liver fibrosis and the potential of its pharmacological inhibition for treatment of hepatic fibrosis.

METHODS: alphavbeta6 expression was studied by quantitative PCR and immunohistochemistry in rats with cirrhosis due to bile duct ligation (BDL), administration of thioacetamide (TAA), in Mdr2(Abcb4)(-/−) mice with spontaneous biliary fibrosis, and in livers of patients with chronic hepatitis C (n=79) and end-stage liver disease due to various etiologies (n=18). The effect of a selective alphavbeta6 inhibitor was evaluated in Mdr2(Abcb4)(−/−) mice with ongoing fibrogenesis.

RESULTS: Integrin beta6 mRNA increased with fibrosis stage in hepatitis C and was upregulated between 25- and 100-fold in TAA- and BDL-induced cirrhosis, in Mdr2(Abcb4)(−/−) mice and in human end-stage liver disease. alphavbeta6 protein was absent in normal livers and expressed de novo on (activated) bile duct epithelia and transitional hepatocytes. A single dose of the alphavbeta6 inhibitor injected into Mdr2(Abcb4)(−/−) mice significantly induced profibrolytic matrix metalloproteinases (MMP)-8 and -9 after 3 h, with a corresponding increase in extracellular...
matrix-degrading activities. In parallel profibrogenic transcripts (procollagen alpha1(I), TGFbeta2, and MMP-2) showed a trend of downregulation. CONCLUSIONS: (1) Integrin alphavbeta6 is induced de novo in rodent and human liver fibrosis, where it is expressed on activated bile duct epithelia and (transitional) hepatocytes during fibrosis progression. (2) In vivo a single dose of a small molecule alphavbeta6 inhibitor induced antifibrogenic and profibrolytic genes and activities, suggesting alphavbeta6 is a unique target for treatment of liver fibrosis.