The TGF-beta1 target WISP1 is highly expressed in liver cirrhosis and cirrhotic HCC microenvironment and involved in pro- and anti-tumorigenic effects.

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Abstract

INTRODUCTION: WNT1-inducible signalling pathway protein 1 (WISP1) promotes progression of several tumor entities often correlating with worse prognosis. Here its expression regulation and role in the progression of chronic liver diseases (CLD) was investigated. METHODS: WISP1 expression was analyzed in human HCC datasets, in biopsies and serum samples and an HCC patient tissue microarray (TMA) including correlation to clinicopathological parameters. Spatial distribution of WISP1 expression was determined using RNAscope analysis. Regulation of WISP1 expression was investigated in cytokine-stimulated primary mouse hepatocytes (PMH) by array analysis and qRT-PCR. Outcome of WISP1 stimulation was analyzed by IncuCyte S3-live cell imaging, qRT-PCR, and immunoblotting in murine AML12 cells. RESULTS: In a TMA, high WISP1 expression was positively correlated with early HCC stages and male sex. Highest WISP1 expression levels were detected in patients with cirrhosis as compared to healthy individuals, patients with early fibrosis, and non-cirrhotic HCC in liver biopsies, expression datasets and serum samples. WISP1 transcripts were predominantly detected in hepatocytes of cirrhotic rather than tumorous liver tissue. High WISP1 expression was associated with better survival. In PMH, AML12 and HepaRG, WISP1 was identified as a specific TGF-beta1 target gene. Accordingly, expression levels of both cytokines positively correlated in human HCC patient samples. WISP1-stimulation induced the expression of Bcl-xL, PCNA and p21 in AML12 cells. CONCLUSIONS: WISP1 expression is induced by TGF-beta1 in hepatocytes and is associated with cirrhotic liver disease. We propose a crucial role of WISP1 in balancing pro- and anti-tumorigenic effects during premalignant stages of CLD.