Targeted disruption of Smad3 confers resistance to the development of dimethylnitrosamine -induced hepatic fibrosis in mice

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Background Hepatic fibrosis is characterized by a progressive accumulation of fibrillar extracellular matrix (ECM) proteins including collagen, which occurs in most types of chronic liver diseases. Transforming growth factor β (TGFβ)/Smad3 signalling plays a central role [1] in tissue fibrogenesis [2], acting as a potent stimulus of ECM accumulation.

Aim to evaluate the potential protective role of Smad3 deficiency in the pathogenesis of liver fibrosis induced by dimethylnitrosamine (DMN) in Smad3 null mice.

Methods Chronic hepatitis-associated fibrosis was induced in 13 Smad3 null and 13 wild type (WT) mice by intraperitoneal DMN administration (10μg/g body weight/day) for 3 consecutive days per week for 6 weeks. The liver was excised for macroscopic examination and histological, morphometric and immunohistochemical (IHC) analyses. For IHC, α smooth muscle actin (SMA), collagen types I-III, TGFβ1, connective tissue growth factor (CTGF), Smad3, Smad7 and CD3 antibodies were used.

Results At macroscopic examination, the liver of DMN-treated Smad3 WT appeared harder with a dark brown colouring and necrotic areas compared with that from null mice. Histological and morphometric evaluation revealed a significantly higher degree of hepatic fibrosis and accumulation of connective tissue in Smad3 WT compared with null mice. IHC evaluation showed a marked increase in αSMA, CTGF, collagen I-III, TGFβ and Smad3 staining in the liver of Smad3 WT compared with that in null mice, whereas Smad7 was increased only in null mice.

Conclusions The results indicate that Smad3 loss confers resistance to the development of DMN-induced hepatic fibrosis. The reduced fibrotic response appears to be due to a reduction of fibrogenic miofibroblast activation and ECM production and accumulation. Smad3 could be a novel target for potential treatment of fibrosis complicating chronic hepatitis.

References

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Key words
Liver fibrosis, DMN induced hepatitis, Smad proteins