Thy-1 restricts steatosis and liver fibrosis in steatotic liver disease

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Abstract

Background and Aims

Steatotic liver disease (SLD) is generally considered to represent a hepatic manifestation of metabolic syndrome and includes a disease spectrum comprising isolated steatosis, metabolic dysfunction-associated steatohepatitis, liver fibrosis and ultimately cirrhosis. A better understanding of the detailed underlying pathogenic mechanisms of this transition is crucial for the design of new and efficient therapeutic interventions. Thymocyte differentiation antigen (Thy-1, also known as CD90) expression on fibroblasts controls central functions relevant to fibrogenesis, including proliferation, apoptosis, cytokine responsiveness, and myofibroblast differentiation.

Methods

The impact of Thy-1 on the development of SLD and progression to fibrosis was investigated in high-fat diet (HFD)-induced SLD wild-type and Thy-1-deficient mice. In addition, the serum soluble Thy-1 (sThy-1) concentration was analysed in patients with metabolic dysfunction-associated SLD stratified according to steatosis, inflammation, or liver fibrosis using noninvasive markers.

Results

We demonstrated that Thy-1 attenuates the development of fatty liver and the expression of profibrogenic genes in the livers of HFD-induced SLD mice. Mechanistically, Thy-1 directly inhibits the profibrotic activation of nonparenchymal liver cells. In addition, Thy-1 prevents palmitic acid-mediated amplification of the inflammatory response of myeloid cells, which might indirectly contribute to the pronounced development of liver fibrosis in Thy-1-deficient mice. Serum analysis of patients with metabolically associated steatotic liver disease syndrome revealed that sThy-1 expression is correlated with liver fibrosis status, as assessed by liver stiffness, the Fib4 score, and the NAFLD fibrosis score.

Conclusion

Our data strongly suggest that Thy-1 may function as a fibrosis-protective factor in mouse and human SLD.