ECM1 attenuates hepatic fibrosis by interfering with mediators of latent TGF-β1 activation

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Abstract

Objective: Extracellular matrix protein 1 (ECM1) serves as a gatekeeper of hepatic fibrosis by maintaining transforming growth factor-β1 (TGF-β1) in its latent form. ECM1 knockout (KO) causes latent (L) TGF-β1 activation, resulting in hepatic fibrosis with rapid mortality. In chronic liver disease (CLD), ECM1 decreases with increasing CLD severity. We investigate the regulatory role of ECM1 in TGF-β1 bioavailability and its impact on CLD progression.

Design: RNAseq was performed to analyse hepatic gene expression. Functional assays were performed using hepatic stellate cells (HSCs), Ecm1-KO and Fxr-KO mice, patient liver tissue and computer simulations.

Results: Expression of LTGF-β1 activators, including thrombospondins (TSPs), ADAMTS proteases and matrix metalloproteinases (MMPs), increased along with profibrotic gene expression in liver tissue of Ecm1-KO mice. In HSCs, overexpression of ECM1 prevented LTGF-β1 activation mediated by TSP-1, ADAMTS1, and MMP-2/9. In vitro interaction assays demonstrated that ECM1 inhibited LTGF-β1 activation by interacting with TSP-1 and ADAMTS1 via their respective, intrinsic KRFK or KTFR amino acid sequences and by suppressing MMP-2/9 proteolytic activity. In mice, ECM1 overexpression attenuated KRFK-induced LTGF-β1 activation while KTFR treatment reversed Ecm1-KO-mediated and Fxr-KO-mediated liver injury. In patients with CLD, ECM1 expression was inversely correlated with TSP-1, ADAMTS1, MMP-2/9 expression and LTGF-β1 activation. And, these results were complemented by a computational compartment model representing the key network of cellular phenotypes and predicted interactions in liver fibrogenesis.

Conclusion: Our findings underscore the hepatoprotective effect of ECM1, which interferes with mediators of LTGF-β1 activation, suggesting ECM1 or its representative peptide as potential antifibrotic therapies in CLD.