ECM1 attenuates hepatic fibrosis by interfering with mediators of latent TGF-beta1 activation.

Info

PUBLIZIERT AM
2025-02-06

JOURNAL
Gut

LINK
https://www.ncbi.nlm.nih.gov/pubmed/39448254

Autoren

F. Link Y. Li J. Zhao S. Munker W. Fan Z. C. Nwosu Y. Yao S. Wang C. Huang R. Liebe S. Hammad H. Liu C. Shao C. Gao B. Sun N. J. Torok H. Ding M. P. Ebert H. Weng P. Ten Dijke D. Drasdo S. Dooley S. Wang

Abstract

OBJECTIVE: Extracellular matrix protein 1 (ECM1) serves as a gatekeeper of hepatic fibrosis by maintaining transforming growth factor-beta1 (TGF-beta1) in its latent form. ECM1 knockout (KO) causes latent (L) TGF-beta1 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-beta1 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-beta1 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-beta1 activation mediated by TSP-1, ADAMTS1, and MMP-2/9. In vitro interaction assays demonstrated that ECM1 inhibited LTGF-beta1 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-beta1 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-beta1 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-beta1 activation, suggesting ECM1 or its representative peptide as potential antifibrotic therapies in CLD.