Extracellular Matrix Protein 1 Attenuates Hepatic Fibrosis by Inhibiting TSP-, ADAMTS-, and MMP-Mediated Latent TGF-β1 Activation

Info

PUBLISHED DATE
2023-12-12

JOURNAL
preprint

LINK
https://doi.org/10.1101/2023.12.12.571289

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Abstract

Objective Extracellular Matrix Protein 1 (Ecm1) knockout results in latent transforming growth factor-β1 (LTGF-β1) activation and hepatic fibrosis with rapid mortality in mice. In chronic liver disease (CLD), ECM1 is gradually lost with increasing CLD severity. We investigated the underlying mechanism and its impact on CLD progression.

Design RNAseq was performed to analyze gene expression in the liver. Functional assays were performed using hepatic stellate cells (HSCs), WT and Ecm1-KO mice, and liver tissue. Computer modeling was used to verify experimental findings.

Results RNAseq shows that expression of thrombospondins (TSPs), ADAMTS proteases, and matrix metalloproteinases (MMPs) increases along with TGF-β1 target, pro-fibrotic genes in liver tissue of Ecm1-KO mice. In LX-2 or primary human HSCs, ECM1 prevented TSP-1-, ADAMTS1-, and MMP-2/9-mediated LTGF-β1 activation. In vitro interaction assays demonstrated that ECM1 inhibited LTGF-β1 activation through interacting with TSP-1 and ADAMTS1 via their respective, intrinsic KRFK or KTFR amino acid sequences, while also blunting MMP-2/9 proteolytic activity. In mice, AAV8-mediated ECM1 overexpression attenuated KRFK-induced LTGF-β1 activation and fibrosis, while KTFR reversed Ecm1-KO-induced liver injury. Furthermore, a correlation between decreasing ECM1 and increasing protease expression and LTGF-β1 activation was found in CLD patients. A computational model validated the impact of restoring ECM1 on reducing LTGF-β1 activation, HSC activation, and collagen deposition in the liver.

Conclusion Our findings underscore the hepatoprotective effect of ECM1, which inhibits protease-mediated LTGF-β1 activation, suggesting that preventing its decrease or restoring ECM1 function in the liver could serve as a novel and safer than direct TGF-β1-directed therapies in CLD.

One sentence summary ECM1 loss fails to prevent TSP/ADAMTS/MMP-mediated LTGF-β1 activation, leading to liver fibrosis progression.