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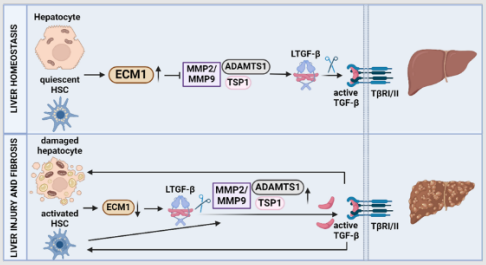
Important Step Toward a Therapy for Liver Fibrosis

ECM1 Inhibits Liver Fibrosis by Targeting Mediators That Convert TGF-β from Its Biologically Inactive Form to Its Active Form

The research group "Molecular Hepatology" from the Dept. of Medicine II., of the University Medical Faculty Mannheim, Heidelberg University, led by Professor Dr. Steven Dooley, has uncovered a significant mechanism involved in liver fibrosis. Their findings have been published in the renowned gastroenterology journal *Gut*. The study highlights the extracellular matrix protein 1 (ECM1) as a central component of potential new therapies aimed at preventing liver fibrosis.

Approximately 5 million people in Germany suffer from chronic liver disease, caused primarily by chronic alcohol consumption, hepatitis virus infection, or fatty liver disease. These conditions damage liver cells (hepatocytes), triggering inflammatory responses. Liver fibrosis is a late-stage consequence of chronic liver damage, characterized by the "scarring" of the liver as liver tissue is replaced by connective tissue, leading to a progressive loss of liver function. Around 500,000 people in Germany are affected by liver fibrosis, for which no effective treatments currently exist.

The mechanism in the graphic



The role of ECM1 in liver homeostasis and injury. In a state of equilibrium, ECM1, which is released by healthy hepatocytes and quiescent hepatic stellate cells (HSCs), prevents the activation of latent TGF-β (LTGF-β) by blocking ADAMTS1, TSP-1, MMP-2, and MMP9. However, during liver injury, the expression of ECM1 by hepatocytes decreases, allowing the activation of LTGF-β by ADAMTS1, TSP-1, MMP-2, and MMP-9 to proceed unchecked. This results in an increase in the concentration of active TGF-β, leading to enhanced activation of HSCs and the deposition of extracellular matrix.

Publication

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ECM1 attenuates hepatic fibrosis by interfering with mediators of latent TGF-β1 activation
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The study was also selected for commentary in the journal Gut:
https://doi.org/10.1136/gutjnl-2024-333455

*Fan et al. Gastroenterology 2019)

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Frederik Link, the lead author of the study, demonstrated as part of his doctoral research, under the guidance and experimental support of Dr. Sai Wang and several collaborators, how ECM1 acts as a "gatekeeper" in a healthy liver to suppress the activation of the signaling molecule transforming growth factor-β (TGF-β).

TGF-β plays a critical role in liver homeostasis and is considered a key driver of liver fibrosis. When TGF-β is converted from its biologically inactive form (LTGF-β) to its active form (TGF-β), it promotes fibrosis by activating hepatic stellate cells (HSCs). These cells transform into myofibroblasts and excessively produce connective tissue. Regulating locally activated TGF-β levels thus represents a promising therapeutic target for preventing liver fibrosis.

As early as 2019, the Mannheim researchers, in collaboration with a Chinese research group in Shanghai, were the first to identify the significant role of ECM1 in the liver. They found that ECM1 maintains TGF-β in its latent form and have since made the protein a focal point of their fibrosis research. In a project funded by the German Research Foundation (DFG), Link and the team led by Sai Wang experimentally identified the mediators involved in this mechanism. These include thrombospondin-1 (TSP-1), ADAMTS protease 1 (ADAMTS1), and matrix metalloproteinases 2 and 9 (MMP-2 and MMP-9). When ECM1 expression in hepatic stellate cells is elevated, the protein blocks the activation of LTGF-β mediated by these factors.

Through in vitro interaction studies, the researchers identified specific four-amino-acid sequences that en-

able ECM1 to interact directly with TSP-1 (sequence: KRFK) and ADAMTS1 (sequence: KTFR). These interactions suppress the proteolytic activity of MMP-2 and MMP-9. The effectiveness of these sequences was confirmed in corresponding mouse model systems. Data from liver tissue of patients with chronic liver disease further supported these findings: ECM1 levels inversely correlated with the expression of the identified mediators and LTGF-β activation.

This new study provides fresh insights into the processes occurring in the damaged liver during chronic liver disease and underscores the protective role of ECM1 for liver health. The identified mechanism offers promising starting points for potential liver fibrosis therapies. The authors have proposed several ideas for how such a therapy could be implemented, which are the subject of ongoing research.