The Interplay of TGF-β1 and Cholesterol Orchestrating Hepatocyte Cell Fate, EMT, and Signals for HSC Activation

Info

PUBLISHED DATE
2024-01-01

JOURNAL
Cellular and Molecular Gastroenterology and Hepatology

LINK
https://doi.org/10.1016/j.jcmgh.2023.12.012

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Abstract

Background & aims

Transforming growth factor-β1 (TGF-β1) plays important roles in chronic liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD). MASLD involves various biological processes including dysfunctional cholesterol metabolism and contributes to progression to metabolic dysfunction-associated steatohepatitis and hepatocellular carcinoma. However, the reciprocal regulation of TGF-β1 signaling and cholesterol metabolism in MASLD is yet unknown.

Methods

Changes in transcription of genes associated with cholesterol metabolism were assessed by RNA sequencing of murine hepatocyte cell line (alpha mouse liver 12/AML12) and mouse primary hepatocytes treated with TGF-β1. Functional assays were performed on AML12 cells (untreated, TGF-β1 treated, or subjected to cholesterol enrichment [CE] or cholesterol depletion [CD]), and on mice injected with adenovirus-associated virus 8-control/TGF-β1.

Results

TGF-β1 inhibited messenger RNA expression of several cholesterol metabolism regulatory genes, including rate-limiting enzymes of cholesterol biosynthesis in AML12 cells, mouse primary hepatocytes, and adenovirus-associated virus-TGF-β1-treated mice. Total cholesterol levels and lipid droplet accumulation in AML12 cells and liver tissue also were reduced upon TGF-β1 treatment. Smad2/3 phosphorylation after 2 hours of TGF-β1 treatment persisted after CE or CD and was mildly increased after CD, whereas TGF-β1-mediated AKT phosphorylation (30 min) was inhibited by CE. Furthermore, CE protected AML12 cells from several effects mediated by 72 hours of incubation with TGF-β1, including epithelial-mesenchymal transition, actin polymerization, and apoptosis. CD mimicked the outcome of long-term TGF-β1 administration, an effect that was blocked by an inhibitor of the type I TGF-β receptor. In addition, the supernatant of CE- or CD-treated AML12 cells inhibited or promoted, respectively, the activation of LX-2 hepatic stellate cells.

Conclusions

TGF-β1 inhibits cholesterol metabolism whereas cholesterol attenuates TGF-β1 downstream effects in hepatocytes.