

TGF- β 1 inhibits cholesterol metabolism in hepatocytes to facilitate cell death, EMT and signals for HSC activation.

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Abstract

Objective: Transforming growth factor- β 1 (TGF- β 1) plays important roles in chronic liver diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), which involves various biological processes including dysfunctional cholesterol metabolism contributing to progression to metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC). However, how TGF- β 1 signaling and cholesterol metabolism affects each other in MASLD is yet unknown. Design: Changes in transcription of genes associated with cholesterol metabolism were assessed by RNA-Seq of AML12 cells and mouse primary hepatocytes (MPH) treated with TGF- β 1. Functional assays were performed on AML12 cells (untreated, TGF- β 1 treated, or subjected to cholesterol enrichment (CE) or depletion (CD)), and on mice injected with adeno-associated virus 8 (AAV8)-Control/TGF- β 1. Results: TGF- β 1 inhibited mRNA expression of several cholesterol metabolism regulatory genes, including rate-limiting enzymes of cholesterol biosynthesis in AML12 cells, MPHs, and AAV8-TGF- β 1-treated mice. Total cholesterol levels in AML12 cells, as well as lipid droplet accumulation in AML12 cells and AAV-treated mice were also reduced. Smad2/3 phosphorylation following 2 h TGF- β 1 treatment persisted after CE or CD and was mildly increased following CD, while TGF- β 1-mediated AKT phosphorylation (30 min) was inhibited by CE. Furthermore, CE protected AML12 cells from several effects mediated by 72 h incubation with TGF- β 1, including EMT, actin polymerization, and apoptosis. CD mimicked the outcome of long term TGF- β 1 administration, an effect that was blocked by an inhibitor of the type I TGF- β receptor. Additionally, the supernatant of CE- or CD-treated AML12 cells inhibited or promoted, respectively, the activation of LX-2 hepatic stellate cells. Conclusion: TGF- β 1 inhibits cholesterol metabolism while cholesterol attenuates TGF- β 1 downstream effects in hepatocytes.