Transforming Growth Factor-β Signaling in Alcohol-Associated Liver Disease

Info

PUBLISHED DATE
2025-10-01

JOURNAL
The American Journal of Pathology

LINK
https://doi.org/10.1016/j.ajpath.2025.09.017

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Abstract

Transforming growth factor-β (TGF-β) signaling exerts broad regulatory effects on alcohol-associated liver disease (ALD) progression, influencing processes such as hepatocellular injury, regeneration, inflammation, fibrogenesis, cirrhosis, carcinogenesis, and hepatic failure. TGF-β modifies alcohol-induced signals in multiple liver-resident cell types, including hepatocytes, hepatic stellate cells, liver sinusoidal endothelial cells, and immune populations, particularly macrophages. To delineate its context-specific roles in ALD, 154 of 421 PubMed-listed publications (2000 to 2025; search terms TGF-β and alcohol and liver disease) were reviewed, supplemented by 19 foundational studies published earlier. In hepatocytes, TGF-β promotes oxidative stress, apoptosis, metabolic reprogramming, and epithelial-to-mesenchymal transition. In hepatic stellate cells and Kupffer cells, gut-derived endotoxins, ethanol, and unsaturated fatty acids induce TGF-β alongside proinflammatory cytokines. Ethanol metabolism generates acetaldehyde, which drives TGF-β and receptor expression, enhances canonical and noncanonical signaling, and engages epigenetic regulators to promote extracellular matrix deposition. In liver sinusoidal endothelial cells, alcohol-induced TGF-β suppresses proliferation, contributing to sinusoidal capillarization, impaired endothelial regeneration, and fibrogenesis. TGF-β dampens clearance of damaged hepatocytes and perpetuating chronic injury by suppressing natural killer cell cytotoxicity and promoting regulatory T-cell differentiation. At end-stage disease, TGF-β promotes expansion and fate switching of cholangiocyte-derived liver progenitor cells to replenish lost hepatocytes. Despite its central role in ALD, therapeutic exploitation of TGF-β signaling remains underexplored. Future studies should define cell type-specific signaling nodes to enable precision therapies.