TGF-β serves as a critical signaling determinant of liver progenitor cell fate and function

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Abstract

Liver progenitor cells (LPCs) are the smallest cholangiocytes that perform hepatocyte functions to rescue the lives of patients suffering from acute liver failure (ALF) caused by massive hepatic necrosis (MHN). To date, it remains largely unknown how LPCs remain quiescent and become activated following MHN. This study elucidates the essential role of TGF-β in regulating LPC quiescence and activation. Spatial transcriptomics analysis of liver tissues from four MHN-ALF patients revealed that LPCs receive multiple active signals from surrounding macrophages and hepatic stellate cells, including TGF-β, HGF, and EGF. Physiologically, TGF-β inhibits LPC proliferation by impeding G1-S phase transition. Ectopic Smad7 expression remarkably increased LPC proliferation in 3,5-diethoxycarbonyl-1,4-dihydrocollidine-fed mice. Intriguingly, extensive LPC proliferation was observed in ALF patients despite robust TGF-β-p-SMAD2 signaling in activated LPCs. Immunohistochemistry and immunofluorescence revealed significantly elevated expression of p-MET, p-STAT3, p-EGFR, and p-ERK in LPCs, indicating active HGF and EGF signaling. In vitro, either HGF or EGF promoted LPC proliferation despite the presence of TGF-β. Beyond acting as mitogens, HGF and EGF regulate master hepatocyte genes (e.g., HNF4α) and cholangiocyte genes (e.g., SOX9) in LPCs. Notably, HGF-dependent HNF4α required TGF-β-activated SMADs. Collectively, TGF-β serves as a critical signaling determinant of LPC fate and function.