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Integration of TGF-β and EGF signaling pathways control liver progenitor cell proliferation in acute liver failure

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Background and Aims: In acute liver failure (ALF), massive hepatic necrosis (MHN) results in severe clinical manifestations and high mortality. Remarkably, liver progenitor cells (LPCs) can rescue ALF in patients through performing vital liver function. To date, key signals that induce LPC proliferation and mediate cellular fate changes allowing gene expression patterns compensating for loss of essential liver functions remains largely unknown. This study aims to investigate how LPCs maintain proliferative quiescence under physiological conditions and how they are activated in ALF towards rapid proliferation.
Methods: SMAD7 transgenic mice were fed with DDC diet to examine the role of TGF-β signaling in LPC proliferation. Spatial transcriptomics was performed on 4 ALF patient liver samples to analyze cell-cell communication between LPCs, hepatocytes and macrophages. Mechanistically, integration of TGF-β and EGF signaling pathways was investigated in the LPC line HepaRG through multiple cellular and molecular approaches, including colony formation, cell cycle analysis, qPCR, Western blot, immunofluorescence staining, and ChIP-qPCR.
Results: Cytostatic TGF-β signaling maintains LPC quiescence under physiological conditions through impeding G1-S phase transition. Overexpression of SMAD7 increases LPC proliferation in DDC-fed mice by inhibiting TGF-β-induced SMAD3 phosphorylation. In ALF, significant levels of TGF-β are still present, provided from activated macrophages, rather than hepatic stellate cells. Interestingly, despite of the presence of TGF-β signaling, in this setting LPCs are proliferating. Mechanistically, EGF signaling effectively inhibits the anti-proliferative TGF-β effect through multiple mechanisms. EGF induces FOXO1 phosphorylation and nuclear exclusion, thereby preventing canonical SMAD-mediated transcription of the cell cycle inhibitors. Additionally, EGF promotes expression of c-MYC, which directly binds to CCND1 gene regulatory regions to drive cyclin D1 expression.
Conclusion: Our study provides novel insights into how LPCs remain non-proliferative in healthy liver and how they may rapidly achieve proliferative activity and take over liver-specific functions following MHN. Cytostatic TGF-β-SMAD signalling physiologically keeps LPC quiescent. In ALF, EGF overrides TGF-β's growth-inhibitory in LPCs.