Follistatin-controlled activin-HNF4α-coagulation factor axis in liver progenitor cells determines outcome of acute liver failure

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Abstract

Background and aims: In patients with acute liver failure (ALF) who suffer from massive hepatocyte loss, liver progenitor cells (LPCs) take over key hepatocyte functions, which ultimately determines survival. This study investigated how the expression of hepatocyte nuclear factor 4α (HNF4α), its regulators, and targets in LPCs determines clinical outcome of patients with ALF.

Approach and results: Clinicopathological associations were scrutinized in 19 patients with ALF (9 recovered and 10 receiving liver transplantation). Regulatory mechanisms between follistatin, activin, HNF4α, and coagulation factor expression in LPC were investigated in vitro and in metronidazole-treated zebrafish. A prospective clinical study followed up 186 patients with cirrhosis for 80 months to observe the relevance of follistatin levels in prevalence and mortality of acute-on-chronic liver failure. Recovered patients with ALF robustly express HNF4α in either LPCs or remaining hepatocytes. As in hepatocytes, HNF4α controls the expression of coagulation factors by binding to their promoters in LPC. HNF4α expression in LPCs requires the forkhead box protein H1-Sma and Mad homolog 2/3/4 transcription factor complex, which is promoted by the TGF-β superfamily member activin. Activin signaling in LPCs is negatively regulated by follistatin, a hepatocyte-derived hormone controlled by insulin and glucagon. In contrast to patients requiring liver transplantation, recovered patients demonstrate a normal activin/follistatin ratio, robust abundance of the activin effectors phosphorylated Sma and Mad homolog 2 and HNF4α in LPCs, leading to significantly improved coagulation function. A follow-up study indicated that serum follistatin levels could predict the incidence and mortality of acute-on-chronic liver failure.

Conclusions: These results highlight a crucial role of the follistatin-controlled activin-HNF4α-coagulation axis in determining the clinical outcome of massive hepatocyte loss-induced ALF. The effects of insulin and glucagon on follistatin suggest a key role of the systemic metabolic state in ALF.