Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Activin drives liver progenitor cells to take over coagulation function through upregulating HNF4α in acute on chronic liver failure

Autor: Tao Lin
Institut / Klinik: Pathologisches Institut
Doktorvater: Prof. Dr. A. Marx

In most circumstances of liver injury, hepatocytes proliferate rapidly, restoring liver mass and maintaining essential functions required to maintain body homeostasis. However, in severe liver diseases with massive hepatocyte loss, such as massive hepatic necrosis (MHN) in acute liver failure (ALF) or submassive hepatic necrosis in acute-on-chronic liver failure (ACLF), the remaining hepatocytes lose their proliferative capacity, or the proliferating hepatocytes cannot restore hepatic mass and maintain essential liver functions. In these life-threatening conditions, liver progenitor cells (LPC) run hepatocyte function largely determines the clinical outcome of patients suffering from massive hepatocyte loss. This study aims to investigate how the LPC take over coagulation function during MHN. In this study, I examined clinical parameters, liver histological alterations and HNF4α expression in ALCF patients, including 5 recovered and 5 liver transplantation patients. The results revealed that compared to the irreversible ACLF patients who demonstrated rather weak immune reactivity for HNF4α in both hepatocytes and LPC, the recovered patients displayed intensive HNF4α immune positivity in the nuclei of either hepatocytes or LPC. In vitro, activin induces HNF4α expression in human and mouse LPC through forming a pSmad2/3-Smad4-FOXH1 complex, which bound to the promoter of HNF4α. Subsequently, HNF4α bound to the promoters of the coagulation factor F2 and F5 genes to induce transcription. Moreover, I found that hepatocytes-derived follistatin, which are regulated by glucagon and insulin, determine the activin-HNF4α-coagulation factor axis in LPC.
In conclusion, my study provides the following main findings: (1) LPC take over and run key hepatocyte functions, e.g. coagulation, in ACLF patients suffering from massive loss of hepatocytes; (2) Expression of coagulation factors in LPC depends on hepatocyte lineage transcription factor HNF4α, which is usually expressed in hepatocytes; (3) HNF4α expression in LPC is driven by activin signal; (4) Whether LPC possess an intact activin-HNF4α-coagulation factor regulatory axis largely determines the clinical outcome of ACLF patients; (5) The activin signaling is negatively regulated by follistatin, a hepatocyte-derived activin inhibitor, which is controlled by the insulin-to-glucagon ratio.