A hierarchical regulatory network ensures stable albumin transcription under various pathophysiological conditions

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Abstract

Background and aims: It remains unknown how patients with liver failure maintain essential albumin levels. Here, we delineate a hierarchical transcription regulatory network that ensures albumin expression under different disease conditions.

Approach and results: We examined albumin levels in liver tissues and serum in 157 patients, including 84 with HCC, 38 decompensated cirrhosis, and 35 acute liver failure. Even in patients with liver failure, the average serum albumin concentrations were 30.55 g/L. In healthy subjects and patients with chronic liver diseases, albumin was expressed in hepatocytes. In patients with massive hepatocyte loss, albumin was expressed in liver progenitor cells (LPCs). The albumin gene (ALB) core promoter possesses a TATA box and nucleosome-free area, which allows constitutive RNA polymerase II binding and transcription initiation. Chromatin immunoprecipitation assays revealed that hepatocyte nuclear factor 4 alpha (HNF4α), CCAAT/enhancer-binding protein alpha (C/EBPα), and forkhead box A2 (FOXA2) bound to the ALB enhancer. Knockdown of either of these factors reduced albumin expression in hepatocytes. FOXA2 acts as a pioneer factor to support HNF4α and C/EBPα. In hepatocytes lacking HNF4α and C/EBPα expression, FOXA2 synergized with retinoic acid receptor (RAR) to maintain albumin transcription. RAR nuclear translocation was induced by retinoic acids released by activated HSCs. In patients with massive hepatocyte loss, LPCs expressed HNF4α and FOXA2. RNA sequencing and quantitative PCR analyses revealed that lack of HNF4α and C/EBPα in hepatocytes increased hedgehog ligand biosynthesis. Hedgehog up-regulates FOXA2 expression through glioblastoma family zinc finger 2 binding to the FOXA2 promoter in both hepatocytes and LPCs.

Conclusions: A hierarchical regulatory network formed by master and pioneer transcription factors ensures essential albumin expression in various pathophysiological conditions.