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Hierarchical regulation of albumin transcription in liver cells under physiologic and pathophysiologic conditions

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In the present study, I aim to delineate the transcription factor network regulating albumin transcription in healthy liver and in response to different pathophysiological challenges. In addition, I investigated the regulation of constitutive HNF4α expression in hepatocytes and its impairment in severe liver diseases such as decompensated cirrhosis or acute liver failure.

My results reveal that there exists a hierarchical transcriptional network in hepatocytes or liver progenitor cells (LPC) to maintain essential albumin levels in liver, as follows: (1) In healthy subjects and patients with chronic liver disease, HNF4α and C/EBPα regulate albumin expression in hepatocytes; (2) In cirrhotic patients lacking HNF4α and C/EBPα expression in hepatocytes, FOXA2 replaces these transcription factors to activate albumin transcription; (3) In patients suffering from massive hepatocyte necrosis, albumin is produced by LPC, where both HNF4α and FOXA2 control albumin transcription; (4) Hedgehog-GLI2 signaling plays a crucial role to induce FOXA2 expression in hepatocytes lacking HNF4α and C/EBPα.

Further, my study provides insight on constitutive HNF4α expression in hepatocytes: (1) HNF4α transcription in hepatocytes requires binding of SMAD2/3 and C/EBPα to its promoter; (2) TGF-β-activated SMAD2/3 complex is an activator of HNF4α transcription. On the other hand, the activated SMAD2/3 complex acts as transcriptional repressor of C/EBPα upon binding to its gene promoter; (3) TGF-β-induced SMAD2/3 binding to the *CEBPA* promoter is inhibited by insulin signaling. Therefore, TGF-β does not lead to the loss of C/EBPα and HNF4α expression under normal conditions in hepatocytes of healthy subjects and patients; (4) In the condition of severe inflammation, however, hepatocytes develop insulin resistance in response to pro-inflammatory TNF-α; (5) In the absence of insulin signaling, C/EBPα and HNF4α are successively inhibited by TGF-β.

In conclusion, my study reveals presence of a hierarchical regulatory network in liver cells to guarantee essential albumin expression that is dependent on the respective physiological and pathophysiological challenges. In short, albumin transcription requires constitutively expressed HNF4α, which is controlled by C/EBPα and SMAD2/3.