Insulin Determines Transforming Growth Factor β Effects on Hepatocyte Nuclear Factor 4α Transcription in Hepatocytes

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Abstract

Loss of hepatocyte nuclear factor 4α (HNF4α) expression is frequently observed in end-stage liver disease and associated with loss of vital liver functions, thus increasing mortality. Loss of HNF4α expression is mediated by inflammatory cytokines, such as transforming growth factor (TGF)-β. However, details of how HNF4α is suppressed are largely unknown to date. Herein, TGF-β did not directly inhibit HNF4α but contributed to its transcriptional regulation by SMAD2/3 recruiting acetyltransferase CREB-binding protein/p300 to the HNF4α promoter. The recruitment of CREB-binding protein/p300 is indispensable for CCAAT/enhancer-binding protein α (C/EBPα) binding, another essential requirement for constitutive HNF4α expression in hepatocytes. Consistent with the in vitro observation, 67 of 98 patients with hepatic HNF4α expressed both phospho-SMAD2 and C/EBPα, whereas 22 patients without HNF4α expression lacked either phospho-SMAD2 or C/EBPα. In contrast to the observed induction of HNF4α, SMAD2/3 inhibited C/EBPα transcription. Long-term TGF-β incubation resulted in C/EBPα depletion, which abrogated HNF4α expression. Intriguingly, SMAD2/3 inhibitory binding to the C/EBPα promoter was abolished by insulin. Two-thirds of patients without C/EBPα lacked membrane glucose transporter type 2 expression in hepatocytes, indicating insulin resistance. Taken together, these data indicate that hepatic insulin sensitivity is essential for hepatic HNF4α expression in the condition of inflammation.