

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

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Abstract

Loss of hepatocyte nuclear factor 4 α (HNF4 α) expression is frequently observed in end-stage liver disease and associated with loss of vital liver functions, thus increasing mortality. Loss of HNF4 α expression is mediated by inflammatory cytokines, such as transforming growth factor (TGF)- β . However, details of how HNF4 α is suppressed are largely unknown to date. Herein, TGF- β did not directly inhibit HNF4 α but contributed to its transcriptional regulation by SMAD2/3 recruiting acetyltransferase CREB-binding protein/p300 to the HNF4 α promoter. The recruitment of CREB-binding protein/p300 is indispensable for CCAAT/enhancer-binding protein α (C/EBP α) binding, another essential requirement for constitutive HNF4 α expression in hepatocytes. Consistent with the in vitro observation, 67 of 98 patients with hepatic HNF4 α expressed both phospho-SMAD2 and C/EBP α , whereas 22 patients without HNF4 α expression lacked either phospho-SMAD2 or C/EBP α . In contrast to the observed induction of HNF4 α , SMAD2/3 inhibited C/EBP α transcription. Long-term TGF- β incubation resulted in C/EBP α depletion, which abrogated HNF4 α expression. Intriguingly, SMAD2/3 inhibitory binding to the C/EBP α promoter was abolished by insulin. Two-thirds of patients without C/EBP α 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 HNF4 α expression in the condition of inflammation.