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Functional Characterization of the Liver-enriched Transcription Factor CREB-H

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We have previously characterized transcription factor LZIP/CREB3 to be a growth suppressor targeted by hepatitis C virus oncoprotein. In search of proteins closely related to LZIP, we have identified a liver-enriched transcription factor CREB-H/CREB3L3. LZIP and CREB-H represent a new subfamily of bZIP factors. CREB-H activates transcription by binding to cAMP responsive element, box B, and ATF6/UPRE-binding element. Interestingly, CREB-H has a putative transmembrane domain and it localizes ambiently to the endoplasmic reticulum.

Proteolytic cleavage that removes the transmembrane domain leads to nuclear translocation and activation of CREB-H. CREB-H activates the promoter of hepatic gluconeogenic enzyme phosphoenolpyruvate carboxykinase. This activation can be further stimulated by cAMP and protein kinase A. CREB-H transcript is exclusively abundant in adult liver. In contrast, the expression of CREB-H mRNA is aberrantly reduced in hepatoma tissues and cells. The enforced expression of CREB-H suppresses the proliferation of cultured hepatoma cells. Taken together, our findings suggest that the liver-enriched bZIP transcription factor CREB-H is a growth suppressor that plays a role in hepatic physiology and pathology.