論文内容の要旨

論文題目：**Studies on Regulatory Mechanisms of Metabolic Gene Expression During Liver Development in Mice**
（マウス肝臓における代謝酵素の発現制御機構の解析）

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The liver is a central organ for numerous metabolic functions in adult, whereas it functions as a major hematopoietic organ in the fetal period. Thus the liver changes its characteristics dramatically during development. While some transcription factors have been identified that involve in liver development, the exact regulatory mechanism of liver development is still poorly understood. C/EBPα is a key transcription factor indispensable for the expression of some metabolic enzymes in perinatal liver. However, as C/EBPα is already expressed in fetal liver, the expression of C/EBPα alone does not account for the dramatic expression of metabolic genes, and hence an additional factor(s) is expected to function cooperatively with C/EBPα. Here, I describe collaboration of two transcriptional factors, FOXO1 and YB-1, with C/EBPα to regulate glucose and ammonia metabolism respectively.

Expression of Foxo1 sharply increased in the perinatal liver and augmented C/EBPα-dependent transcription. Foxo1 bound C/EBPα via its forkhead domain, and bound to the promoter of a gluconeogenic gene, phosphoenolpyruvate carboxykinase (PEPCK), in a C/EBPα-dependent manner. Insulin is a negative regulator of gluconeogenesis and suppressed the C/EBPα-dependent transcription of PEPCK via inhibition of Foxo1.

YB-1, a member of the Y-box binding proteins, was known to play a critical role for expression of genes involved in cell proliferation and drug-resistance. While it is also considered as a tumor marker for hepatocellular carcinoma, the YB-1 function in the normal liver remains unknown. Here, I show that YB-1 regulates ammonia metabolism by modulating transcription of the CPS1 gene that encodes a key enzyme in urea cycle. YB-1 expression was evident in the liver at embryonic day 14.5, and declined along with liver maturation. Forced expression of YB-1 in fetal liver cells resulted in suppression of CPS1 expression. YB-1 bound to a Y-box in the CPS1 promoter, down-regulating the transcriptional activity induced by C/EBPα. Moreover, CCl_4-induced liver injury up-regulated YB-1 expression, accompanying the suppression of CPS1 and increase of serum ammonia. Chromatin immunoprecipitation assays showed that YB-1 bound to the CPS1 promoter in fetal and CCl_4-injured livers but not in normal adult liver.

In conclusion, these results indicate that the Foxo1 and YB-1 molecules contribute to the transcriptional regulation of PEPCK and CPS1 genes by modulating C/EBPα activity.