Role of hepatic CRTC2 in the control of systemic energy metabolism

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Liver is a major organ that controls energy homeostasis in mammals. Under the fasting conditions, hepatic glucose production is increased to provide fuels for critical organs such as brain and other peripheral tissues. Enhanced glucose production is achieved by activation of both glycogenolysis and gluconeogenesis. Interestingly, activation of gluconeogenesis is mainly achieved by a transcriptional mechanism in response to pancreatic glucagon and adrenal glucocorticoid. Glucocorticoid signals through a glucocorticoid receptor, and glucagon elicits its effects by inducing cAMP-dependent pathway by using CREB and CREB regulated transcription coactivator 2 (CRTC2) as proximal transcriptional complex. We have previously shown that hyperglycemia under type 2 diabetes was in part mediated by hyperactivation of CREB/CRTC2 signals, which results in uncontrolled glucose production from the liver. To further delineate the mechanistic insight into the role of CRTC2 in the control of energy metabolism, we performed in vivo experiments by using CRTC2 liver-specific knockout mice. Surprisingly, we observed that hepatic depletion of CRTC2 in mice resulted in the improved glucose and lipid homeostasis under DIO conditions. In this talk, we would like to discuss the mechanistic insight of this mouse model in detail.