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Cistromic analysis reveals novel insights into hepatic CREB regulatory mechanisms

The liver is a central organ in the maintenance of blood glucose homeostasis throughout the normal feeding/fasting cycle, and disruption of this homeostatic function is a contributing factor in a number of metabolic diseases1. In mammalian systems, a drop in blood glucose triggers the release of the hormone glucagon, which triggers the production of cAMP in liver hepatocytes2. The cAMP-Response Element Binding protein (CREB) was initially identified as a primary effector of transcriptional changes in response to cAMP signaling3. In particular, CREB has been shown to be a major regulator of fasting-induced hepatic gluconeogenesis4, but the precise molecular mechanisms by which CREB achieves functional specificity in different physiological contexts remain to be elucidated. Increased cAMP levels have been shown to activate Protein Kinase A, which phosphorylates CREB on Serine 133, thereby promoting interactions between CREB and transcriptional co-activators2. In vitro studies have also suggested that phosphorylation of S133 promotes CREB binding to specific DNA sequences5, providing a potential mechanism by which cAMP induces the expression of some CREB target genes, but not others. CREB has also been shown to respond to a number of other signaling pathways, and regulate a broad array of gene transcription programs in different tissues2. Thus, CREB remains an interesting potential therapeutic target in the treatment of metabolic diseases, but challenges remain in specifically targeting the downstream gluconeogenic program.