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Coactivator P300 regulates FOXO1 expression at transcriptional and post-transcriptional levels

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Abstract

The transcriptional factor, FOXO1 plays an important role in regulating both glucose and lipid metabolism. In the fed state, high serum insulin levels phosphorylate FOXO1 through an AKT-dependent mechanism, leading to its nuclear exclusion and degradation in the cytoplasm. However, it remains unclear how FOXO1 expression is controlled in the fasting state, where it functions to increase hepatic gluconeogenesis and maintains euglycemia. Given that acetylation of FOXO1 by p300 facilitates its phosphorylation by AKT, we sought to examine the role of p300 in regulating FOXO1 expression. Adenoviral shRNA was used to deplete p300 in a mouse hepatoma cell line (H2.35), and we found that depletion of p300 resulted in a significant decrease in FOXO1 protein levels. In contrast, adenoviral shRNA depletion of cofactors related to p300 such as CBP and CRTC2 had no effect on the FOXO1 protein levels. Similar results were observed in primary mouse hepatocytes. Compared to the fed state, we found a dramatic increase in mouse hepatic FOXO1 mRNA and protein levels in the fasting state. To test whether p300 regulates *Foxo1* expression at the transcriptional level, we constructed a luciferase reporter construct containing 2.0 kb of *Foxo1* promoter. Co-transfection of p300 led to a 4-fold increase in reporter activity in H2.35 cells, which was further augmented after the addition of a cAMP analogue. Subsequently, we generated a series of promoter deletion constructs and found that p300 activates *Foxo1* transcription by binding to the proximal promoter region. Interestingly, inhibition of p300 histone acetyltransferase activity by C646 also significantly decreased FOXO1 protein levels in H2.35 cells. Our data suggest that p300 controls mRNA expression of *Foxo1* by mediating the glucagon-cAMP effect. P300, however, also increases the amount of FOXO1 protein by acetylating and stabilizing FOXO1 protein levels. By both increasing the amount and stability of FOXO1, hepatic glucose production is maximized during fasting by p300.

Biography

Ling He is an Associate Faculty Member who works with Faculty Member Fredric Wondisford to recommend the scientific literature in their field. Ling He also has responsibility for checking the contents of the following journals to ensure that the highest quality research relevant to their own interests within these publications is comprehensively and systematically evaluated for F1000