Energy availability signals and the prohormone convertase 1 gene are regulated by Nhlh2

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Abstract

Body weight is controlled by gene regulation through the activation of signal transduction pathways which ultimately regulate transcription factors and their gene targets. Fluctuating leptin levels regulate hypothalamic pathways controlling the body's response to energy availability fluctuations. The Nescient basic helix-loop-helix transcription factor 2 (Nhlh2) is a target of leptin stimulation in proopiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus. POMC is cleaved by prohormone convertase 1 (PC1) to α-melanocyte stimulating hormone (αMSH) regulating the body's response to leptin signals. ^ Nhlh2 knockout (N2KO) mice display adult-onset obesity starting at 12 weeks of age characterized not by hyperphagia, but by reduced activity levels. In this dissertation, studies examining the role of Nhlh2 during energy deficit show that N2KO mice have altered leptin, body weight and temperature responses. Nhlh2 likely regulates the transcription of many genes that lead to the development of obesity in N2KO mice. Using microarray technology, more than 7,000 genes that are differentially regulated between WT and N2KO mice in varying energy availability states are reported herein. Previous work in the lab showed that N2KO mice have a POMC processing defect caused by reduced PC1 levels leading to decreased αMSH and increased pro-forms of POMC. Here, new work shows that Nhlh2 binds to and transactivates the PC1 promoter through two putative E-box motifs. These E-box motifs are adjacent to two putative STAT3 transcription factor binding sites. In this work, STAT3 is shown to interact with Nhlh2 at these E-box motifs to regulate PC1. ^ This research further characterizes the obesity phenotype of N2KO mice and the method by which Nhlh2 regulates PC1. This work has identified a new purpose for Nhlh2 in modulating leptin levels following changes in energy availability, and has identified a novel synergism between Nhlh2 and

STAT3 to control basal and induced levels of PC1 in the hypothalamus. Finally, I have identified over 4000 potential targets of Nhlh2 downstream of leptin stimulation which can be analyzed in the future. In summary, work presented in this dissertation provides new insight into the role of Nhlh2-mediated gene regulation and the downstream effects on energy availability signals. ^

Subject Area

Biology, Molecular|Biology, Cell

Recommended Citation