Histone deacetylase 3 regulates neuronatin expression

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Neuronatin (NNAT) is a small proteolipid which is involved in brain development, glucose-mediated insulin secretion from the pancreas, adipogenesis, and metabolic regulation. Therefore, NNAT plays a role in several diseases includes diabetes, cancer, obesity, Lafora disease, and retinal degeneration. Genetic disruption of NNAT in mice enhances inguinal adipose tissue thermogenesis (Previously published in: Choi KM et al. (2023) Mol Metab Mar:69:101679). The aim of this project is to understand the molecular regulation of NNAT transcription and mRNA stability in order to uncover new mechanisms that can be exploited to ameliorate metabolic disorders. Histone deacetylase 3 genetic inactivation (Hdac3fatKO mice) causes a metabolic rewiring in WAT towards browning via activation of a futile cycle of fatty acid metabolism (Previously published in: Ferrari A et al. (2017) Nat Commun 8, 93). RNAseq and ChIPseq analyses revealed that *Nnat* expression is downregulated (-97-fold change) and that a hypoacetylated region upstream of the transcription start site (TSS) of *Nnat* is present in Hdac3fatKO mice compared to controls. Interestingly, preliminary *in silico* analysis predicted the presence in this region of transcription factor binding sites (TFBSs) for KLF4, TLX1 and TAL1, TFs involved in adipocyte differentiation and chromatin remodeling. Accordingly, *Nnat* expression is increased in early stages of primary murine adipocyte differentiation. Furthermore, mmu-miR-708-5p, involved in the degradation of *Nnat* mRNA, is overexpressed in Hdac3fatKO mice. This observation is consistent with the presence of five hyperacetylated regions around its TSS. In conclusion, HDAC3 regulates the miR-708-5p which affects NNAT levels and might also act non-canonically as a coactivator of *Nnat*. A better understanding of the molecular regulation of NNAT could disclose new pathways for the treatment of metabolic syndromes and obesity.