Neuronal gene repression in Niemann-Pick type C models is mediated by the c-Abl-HDAC2 signaling pathway

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Abstract

Background: Niemann–Pick type C (NPC) disease is a fatal neurodegenerative disorder characterized by the accumulation of free cholesterol in lysosomes. There are currently no effective FDA-approved treatments for NPC, although in the last years the inhibition of histone deacetylases (HDACs) has emerged as a potential treatment for this disease. However, the molecular mechanisms that deregulate HDAC activity in NPC disease are unknown. Previously our group had shown that the proapoptotic tyrosine kinase c-Abl signaling is activated in NPC neurons. Here, we demonstrate that c-Abl activity increases HDAC2 levels inducing neuronal gene repression of key synaptic genes in NPC models.ResultsOur data show that: i) HDAC2 levels and activity are increased in NPC neuronal models and in Npc1−/− mice; ii) inhibition of c-Abl or c-Abl deficiency prevents the increase of HDAC2 protein levels and activity in NPC neuronal models; iii) c-Abl inhibition decreases the levels of HDAC2 tyrosine phosphorylation; iv) treatment with methyl-β-cyclodextrin and vitamin E decreases the activation of the c-Abl/HDAC2 pathway in NPC neurons; v) in vivo treatment with two c-Abl inhibitors prevents the increase of HDAC2 protein levels in the brain of Npc1−/− mice; and vi) c-Abl inhibition prevents HDAC2 recruitment to the promoter of neuronal genes, triggering an increase in their expression. Conclusion: Our data show the involvement of the c-Abl/HDAC2 signaling pathway in the regulation of neuronal gene expression in NPC neuronal models. Thus, inhibition of c-Abl could be a pharmacological target for preventing the deleterious effects of increased HDAC2 levels in NPC disease..