c-Abl links APP-BACE1 interaction promoting APP amyloidogenic processing in Niemann-Pick type C disease

Yanez, M. J., Belbin, O., Estrada, L. D., Leal, N., Contreras, P. S., Lleó, A., ... & Alvarez, A. R. (2016). c-Abl links APP-BACE1 interaction promoting APP amyloidogenic processing in Niemann-Pick type C disease. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1862(11), 2158-2167. <10.1016/j.bbadis.2016.08.016> Accessed 26 Nov 2020.

Abstract

Background Niemann-Pick type C (NPC) disease is characterized by lysosomal accumulation of cholesterol. Interestingly, NPC patients' brains also show increased levels of amyloid-β (Aβ) peptide, a key protein in Alzheimer's disease pathogenesis. We previously reported that the c-Abl tyrosine kinase is active in NPC neurons and in AD animal models and that Imatinib, a specific c-Abl inhibitor, decreased the amyloid burden in brains of the AD mouse model. Active c-Abl was shown to interact with the APP cytosolic domain, but the relevance of this interaction to APP processing has yet to be defined. Results In this work we show that c-Abl inhibition reduces APP amyloidogenic cleavage in NPC cells overexpressing APP. Indeed, we found that levels of the Aβ oligomers and the carboxy-terminal fragment βCTF were decreased when the cells were treated with Imatinib and upon shRNA-mediated c-Abl knockdown. Moreover, Imatinib decreased APP amyloidogenic processing in the brain of an NPC mouse model. In addition, we found decreased levels of βCTF in neuronal cultures from c-Abl null mice. We demonstrate that c-Abl directly interacts with APP, that c-Abl inhibition prevents this interaction, and that Tyr682 in the APP cytoplasmic tail is essential for this interaction. More importantly, we found that c-Abl inhibition by Imatinib significantly inhibits the interaction between APP and BACE1. Conclusion We conclude that c-Abl activity facilitates the APP-BACE1 interaction, thereby promoting amyloidogenic processing of APP. Thus, inhibition of c-Abl could be a pharmacological target for preventing the injurious effects of increased Aβ levels in NPC disease..