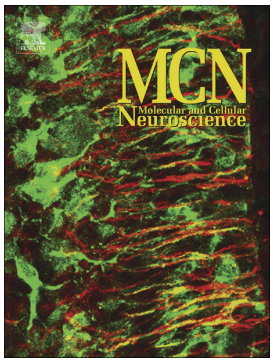

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Defective mitochondrial and lysosomal trafficking in Chorea-Acanthocytosis is independent of Src-kinase signaling

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Abstract

Mutations in the VPS13A gene leading to depletion of chorein protein are causative for Chorea Acanthocytosis (ChAc), a rare devastating disease, which is characterized by neurodegeneration mainly affecting the basal ganglia as well as deformation of erythrocytes. Studies on patient blood samples highlighted a dysregulation of Actin cytoskeleton caused by downregulation of the PI3K pathway and hyper-activation of Lyn-kinase, but to what extent these mechanisms are present and relevant in the affected neurons remains elusive. We studied the effects of the absence of chorein protein on the morphology and trafficking of lysosomal and mitochondrial compartments in ChAc patient-specific induced pluripotent stem cell-derived medium spiny neurons (MSNs). Numbers of both organelle types were reduced in ChAc MSNs. Mitochondrial length was shortened and their membrane potential showed significant hyperpolarization. In contrast to previous studies, showing Lyn kinase dependency of ChAc-associated pathological events in erythrocytes, pharmacological studies demonstrate that the impairment of mitochondria and lysosomes are independent of Lyn kinase activity. These data suggest that impairment in mitochondrial and lysosomal morphologies in MSNs is not mediated by a dysregulation of Lyn kinase and thus the pathological pathways in ChAc might be – at least in part – cell-type specific.

Keywords