The Roles of HAP40 in Mitochondrial Dysfunction of HD Model Cells

Zih-Ning Huang (黃梓甯), Her Min Chung (曾慧明), Zi-Han Huang (黃子瀚), and Lu-Shiun Her (何盧勳)*

Department of Life Sciences, National Cheng Kung University, Tainan 70101, Taiwan
lsher@mail.ncku.edu.tw

Abstract

Huntington's disease (HD) is a progressive neurodegenerative disorder caused by an N-terminal expansion of polyglutamine stretch (polyQ) of huntingtin (Htt) protein. The abnormal polyQ stretch of mutant Htt makes it prone to aggregation, leading to neuropathology which includes proteotoxicity and abnormal mitochondrial dynamics and functions. HAP40 (Huntingtin associated protein 40) is a 40 kDa protein that interacts with Htt. The molecular and cellular functions of HAP40 has not been identified yet. Moreover, the relationship between the expression levels of HAP40 protein and HD etiology remains elusive. HAP40 protein has been shown to increase in HD patients and HD mouse model cells. However, recent proteomic analysis provides new evidence that HAP40 protein is decreased in the striatum of HD knockin model mice. We developed HAP40-specific antibody and showed that both HAP40 mRNA and its encoded protein were reduced in HD striatal neuronal ST*HDH*$^{Q111/Q111}$ cells. Subcellular analysis revealed that, like Htt, a fraction of HAP40 localizes in mitochondria. Interestingly, either overexpression or reduction of HAP40 impairs mitochondria dynamics and functions that subsequently lead to cytotoxicity. It is not clear why both elevation and reduction of HAP40 protein affect the mitochondria system. However, it is important to note that elevation and reduction of HAP40 protein act in different pathways to impact the mitochondria system. Further experiments are required to dissect the effects of HAP40 level on HD etiology.

Keywords – Huntington's disease, HAP40, mitochondrial dynamics