The role of palmitoylation in the pathogenesis of Huntington disease

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Huntington disease (HD) is an adult onset fatal neurodegenerative disease caused by a CAG expansion in exon 1 of the huntingtin gene (HTT). HD is characterized by primary degeneration of medium spiny neurons of the striatum resulting in motor, cognitive and psychiatric deficits followed by death on average 15 years after symptom onset. Huntingtin interacting protein 14 (HIP14, zDHHC17) and huntingtin interacting protein 14-like (HIP14L, zDHHC13) interact with and are the two primary palmitoyl acyl transferases (PATs) for HTT. HTT is not only a substrate of HIP14 but actually modulates the enzymatic activity of HIP14. In the presence of the HD mutation, the interaction between HTT (mHTT) and HIP14 or HIP14L is reduced, resulting in increased neuronal toxicity and in reduced palmitoylation of not only HTT but also of other HIP14 and HIP14L substrates. Palmitoylation of proteins is important for their trafficking and function, so aberrant palmitoylation of HIP14 and HIP14L substrates may lead to mislocalization and altered function. In fact, mice lacking Hip14 or Hip14l develop some features of HD, including motor deficits and striatal atrophy, and mice lacking both genes are embryonic lethal as are mice lacking the Htt gene. Thus, disturbed HIP14/HIP14L-HTT interaction reduces their enzymatic function leading to underpalmitoylation and mislocalization of key substrates, which may contribute to the pathogenesis of HD.