Investigation of Autophagy in Huntington's Disease using a Mutant Huntingtin Knock-in Striatal Cell Line

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Autophagy is implicated in the pathogenesis of Huntington’s disease (HD), a fatal neurodegenerative disorder, and is unproductive in HD cells. This research focused on understanding cellular dysfunction in HD cells with respect to the autophagic pathway by elucidating the relationship between the huntingtin protein and vesicular trafficking, determining the roles of lysosomal positioning and autophagosome-lysosome fusion in HD pathogenesis, and correcting localization abnormalities. The project connected HD, the mutant huntingtin protein (mHtt), and autophagy by analyzing differences between model HD STHdhQ111 and normal STHdhQ7 cells in terms of the localization of autophagosomes and lysosomes, quantities of autophagosomes, intracellular migration of lysosomes resulting from transfection of STHdhQ7 cells or STHdhQ111 cells with mHtt145Q or Htt23Q plasmids respectively, and lysosomal localization correction via exposure to Trichostatin A (TSA). Using serum starvation, TSA exposure, transfection, immunofluorescence, and clustering index analysis, the data showed premature autophagosome-lysosome fusion in STHdhQ111 cells, increased perinuclear lysosomal localization in STHdhQ111 cells relative to lysosomal localization in STHdhQ7 cells, lysosomal anterograde migration in STHdhQ111 cells transfected with Htt23Q, and lysosomal relocation and localization correction in STHdhQ111 cells resulting from TSA exposure. This research provided insight into the molecular mechanisms of HD, revealed the importance of abnormal lysosomal positioning and premature autophagosome-lysosome fusion in causing neurodegeneration, and demonstrated potential for autophagy-based therapeutic strategies.