Tackling autophagy and apoptosis for the potential therapy of Huntington’s Disease

https://www.neurodegenerationresearch.eu/survey/tackling-autophagy-and-apoptosis-for-the-potential-therapy-of-huntingtons-disease/

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United Kingdom

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Tackling autophagy and apoptosis for the potential therapy of Huntington's Disease

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MRC

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3.0

The project/programme is most relevant to:

Huntington's disease

Keywords
Research Abstract

Huntingtin’s Disease (HD) is a progressive neurodegenerative disorder, caused by mutant huntingtin gene (htt) with expanded CAG repeats, which are translated into expanded polyglutamine (polyQ) stretch. The expanded polyQ forms toxic aggregates that induce neuronal death. It has been well characterised that mutant Htt (mHtt) aggregates can be degraded by autophagy, a lysosome-dependent bulk degradation system, and autophagy

upregulation ameliorates HD and other neurodegenerative diseases. Autophagy consists of autophagosome synthesis (cargo delivery) and autophagosome-lysosome fusion (cargo degradation). The initiation of autophagosome synthesis is tightly regulated by a set of autophagy genes, such as Atg1, Beclin 1 and class III PI-3 kinase Vps34. The Beclin 1-Vps34 localisation at ER is critical for the formation of autophagosomes. We found that pro-apoptotic protein Bim restricts Beclin 1-Vps34 complex to microtubules away from its functional site ER, thereby suppressing autophagy. Bim is therefore a dual regulator that promotes apoptosis but inhibits autophagy. Our preliminary data show that the protein and mRNA levels of Bim were significantly enhanced in human HD post-mortem striatum, confirming previous data that Bim levels are increased in HD mouse and cell models. Collectively, these suggest that Bim may a driving factor to progression of HD pathology. We observed that depletion of Bim with RNA interference significantly reduced mutant Htt aggregation and toxicity in cells. Importantly, a peptide derived from Bim (Bim-P) promotes autophagy by antagonising Bim's autophagy inhibition, and reduces mutant Htt aggregation and toxicity in HD in vitro. Based on the preliminary data, we will establish the mechanism by which Bim is upregulated in HD, examine the effect of Bim in HD progression in vivo using HD mouse models and test the efficacy of the Bim-P in treating the HD mouse models.

Lay Summary
Further information available at:

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Investments > €500k

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