

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

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

Principal Investigators

Dr S Luo

Institution

University of Plymouth

Contact information of lead PI Country

United Kingdom

Title of project or programme

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

Source of funding information

MRC

Total sum awarded (Euro)

€ 569,457

Start date of award

01/01/2016

Total duration of award in years

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 be 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:

Types:

Investments > €500k

Member States:

United Kingdom

Diseases:

Huntington's disease

Years:

2016

Database Categories:

N/A

Database Tags:

N/A