Role of Beclin1 in Huntington pathogenesis

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Huntington Disease (HD) is autosomal dominant disorder caused by the polyglutamine (polyQ) expansions of the exon1 in the region of mutated huntingtin protein (mHTT) (1). The mHTT protein produced by aberrant splicing of mutant HTT mRNA. This is the most aggregation-prone species, accumulates in the brains of HD patients and is sufficient to induce severe HD-like pathology (2). Formation of amyloid fibrils from soluble protein involves several intermediate species such as oligomers and aggregates. The importance of these oligomers with respect to disease progression and its toxicity to cells is debatable but mostly they are linked to cytotoxicity (3). Autophagy is critical and important process which help in clearing the toxic protein aggregates in the cells.

Cells use selective autophagy process to clear the mHtt aggregates and found to be protective against HD in cells and animal models (4). Impairment of autophagic activity at different stages can lead to severe HD pathology. While stimulating autophagy improve the neurotoxic effect of HD (5). Beclin1 is one of the important master regulators of autophagy discovered in 1990s and age-dependent decrease of *beclin1* is associated with HD. Interestingly, reduction of Beclin1 expression compromises the autophagosome formation and increases the accumulation of the mHtt (6).

Here in this current study, we wanted to understand how Beclin1 interacts with mHtt and target autophagy? Does Beclin1 has preference for recognize between monomers, toxic oligomers or fibrils? Our results indicate that; indeed, Beclin1 not only binds to monomer huntingtin (100Q) but also with mHtt fibrils. Initial ThT assay results of mHTT indicate typical fibril formation kinetics and which is affected by addition of Beclin1. The idea here is to get structural understanding between Beclin1 binding with mHTT monomer before it starts forming oligomer or fibrils. The kinetic and structural details will be presented in the poster.

References:

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