MOLECULAR CHAPERONES AS A THERAPEUTIC APPROACH TO HUNTINGTON'S DISEASE

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ABSTRACT

Neuronal cell death in subpopulations of brains affected by Huntington's disease has been theorised to be due to cell cytotoxicity. The cause of this cytotoxicity, however, is not yet known. One mutant allele of the Huntingtin gene is sufficient to cause the disorder through the synthesis of the Huntingtin protein. Despite the ubiquitous expression of the HTT gene, expansion of the polyglutamine (polyQ) tract in HTT leads to progressive cell death in affected brains, predominantly in the basal ganglia. The polyQ of the protein expressed when this mutant gene is translated has shown to increase the chance of protein aggregates forming. In the Centre for Genomic Regulation, the transformation and study of S.cerevisiae cells have demonstrated a positive correlation between the number of polyQ repeats and the number of protein aggregates that develop within cells. This was evident in the Western Blot and confocal microscopic images. An extra protein band in the Western Blot indicated protein aggregation in the well with the highest number of CAG repeats, implying that with more repeats, the higher the propensity for aggregation. The growth observed in these cells was slower, indicating the inextricable link between aggregation and cytotoxicity within cells. The detrimental effect of protein aggregation is known, therefore the methods that will be proposed will consist of preventing or reducing protein aggregation within cells. HTT is a functional protein, essential to brain development and neuronal survival and thus, by targeting only the aggregates, the functionality of the protein is not affected. Harnessing the essential role of molecular chaperones in promoting the refolding of proteins within cells will form the main body in discussing a therapeutic approach to Huntington's disease; by studying the aggregation propensity in different concentrations of a molecular chaperone, the effectiveness of the molecule can be investigated. Following the results, a discussion on how effectively this method combats aggregation will follow. This discussion depends on the cytotoxicity that remains in the cells studied.

Keywords*: aggregates; cytotoxicity; heat shock response; huntingtin; molecular chaperones; polyglutamine*

JEL Classification*: I1, I10*