Investigation of the mechanism by which huntingtin fragments are produced and their pathogenic relevance to Huntington’s disease

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United Kingdom

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Research Abstract

Huntington’s disease (HD) is an inherited late onset neurodegenerative disorder caused by a CAG repeat expansion in the HTT gene that leads to an extra long polyglutamine tract in the huntingtin (HTT) protein. Considerable evidence has accumulated to indicate that N-terminal fragments of mutant HTT are pathogenic and may trigger the disease process. We have recently identified a novel mechanism by which a small HTT fragment is generated. We found

that the HD mutation leads to incomplete splicing of HTT exon 1 to exon 2, resulting in a small polyadenylated exon 1-intron 1 mRNA that is translated to produce an exon 1 HTT protein. This may have considerable implications for HD pathogenesis as exon 1 HTT fragments have been found to be highly pathogenic in multiple model systems. SRSF6 is a splicing factor that recognises a CAG repeat sequence and modulates splicing and premature polyadenylation. We shall use molecular biology approaches to further investigate the role of SRSF6 in the aberrant splicing of HTT and identify other splicing factors that may contribute to this process. We shall use zinc finger nuclease technology to produce a model in which the exon 1 HTT protein cannot be generated by mis-splicing and use this to determine the extent to which this small HTT fragment contributes to HD pathogenesis. Finally, we shall use chemical modification and mass spectrometry to determine the identity of additional larger HTT fragments. Huntingtin is a validated therapeutic target for HD. Understanding the contribution that exon 1 HTT makes to disease pathogenesis is essential. A considerable effort is currently being directed at using gene therapy approaches to lower the levels of HTT, not all of which prevent the production of the exon 1-intron 1 mRNA. A complete understanding of HTT gene processing and the production of HTT fragments is a basic requisite to unraveling HD pathogenesis and may lead to novel therapeutic strategies.

Further information available at:

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