



SEMINARIO

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Huntington’s disease as a tauopathy

ABSTRACT

Tauopathies are a group of neurodegenerative diseases such as Alzheimer’s disease, progressive supranuclear palsy, corticobasal degeneration, Pick’s disease, or frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17) that are characterized by altered metabolism and deposition of the microtubule associated protein tau. Alternative splicing of exon 10 of the microtubule-associated protein tau (*MAPT*) gene results in tau isoforms containing either three or four microtubule-binding repeats (3R and 4R, respectively). Discovery of silent and intronic mutations leading to an increased 4R/3R ratio in families affected by FTDP-17 revealed that an imbalance in 4R and 3R in favor of the 4R isoform is sufficient to cause neurodegeneration with personality disturbances, dementia and motor dysfunction.

Huntington’s disease (HD) belongs to the group of dominant trinucleotide repeat diseases that include many other CAG repeat disorders such as the spinocerebellar ataxias SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17, dentatorubropallidoluysian atrophy (DRPLA) and spinobulbar muscular atrophy (SBMA) as well as the CUG repeat disorders SCA8 and myotonic dystrophy 1 (DM1). A key element in the pathogenesis of the latter is the binding of splicing factors by the mutant CUG transcript, thus leading to alternative splicing aberrations in multiple genes. Notably, CAG repeats have recently been shown to mimic CUG repeats in the misregulation of alternative splicing. As it has also been very recently reported that aberrant splicing contributes to the generation of the highly toxic short N-terminal species of HTT, it is conceivable that splicing alterations significantly contribute to HD pathogenesis.

Here we report a 4R/3R tau isoform disbalance at the mRNA and protein level and increased total tau levels in the brains of Huntington’s disease (HD) subjects together with rod-like tau deposits along neuronal nuclei. These tau-nuclear rods (TNRs) show ordered filamentous ultrastructure and can be found filling the neuronal nuclear indentations previously reported in HD brains. Finally, alterations in the splicing factor SRSF6 coincide with tau-missplicing and a role of tau in HD pathogenesis is evidenced by the attenuation of motor abnormalities of HD transgenic mice in tau knock-out backgrounds. These data suggest that therapies aimed to correct tau imbalance in Alzheimer’s disease and other tauopathies might also be useful for HD.

PUBLICATIONS

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