Lack of association between TDP-43 pathology and tau mis-splicing in Alzheimer's disease

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A proportion of Alzheimer's disease cases displays inclusions of the RNA-binding protein, TDP-43. Considering the pathogenic role of tau mis-splicing, we compared tau isoform expression between Alzheimer's disease cases with or without TDP-43 inclusions. The average ratio of tau isoforms containing or lacking exon 10 (4R/3R ratio) or the total level of tau mRNA was not significantly different between cases with or without TDP-43 pathology in any of the brain regions examined. Although TDP-43 functions may be affected, TDP-43 does not critically regulate expression or splicing of tau in Alzheimer's disease suggesting that TDP-43 contributes to Alzheimer's disease through mechanisms independent of tau.

1. Introduction

Alzheimer's disease (AD) is characterized by Aβ and tau pathologies in affected brain areas. In addition, 20%–30% of AD cases display cytoplasmic inclusions of transactive response DNA-binding protein of 43 kDa (TDP-43). The presence of TDP-43 inclusions in the hippocampus and entorhinal cortex correlates with neuronal loss in late onset dementia and, furthermore, a strong correlation exists between the presence of TDP-43 pathology and specific clinical features of AD, especially impaired cognition and amnesia (Davidson et al., 2011). TDP-43 is a predominantly nuclear protein that regulates RNA splicing and stability of multiple targets; therefore, mislocalization and aggregation of TDP-43 could contribute to pathogenesis in a subgroup of AD cases by affecting directly or indirectly the level of expression or splicing of specific targets. As mis-splicing of tau exon 10 (E10) can be pathogenic (Niblock and Gallo, 2012), we compared tau expression and splicing in affected brain regions in AD patients with or without TDP-43 pathology to establish a possible contribution of abnormal TDP-43 activity in AD through tau splicing.

2. Methods

Frozen brain tissue was obtained from individuals free from neurological disease and individuals with AD and controls. Cases were assessed for TDP-43 pathology by immunocytochemistry. RNA was extracted using the QIAGEN RNeasy/lipid kit (QIAGEN). Tau E10 splicing was analyzed by end-point reverse transcription polymerase chain reaction using a forward primer 5'-labelled with an infrared fluorescent dye, yielding a signal independent of the length of the individual products. Gels were imaged, and polymerase chain reaction products were quantified using an Odyssey Infrared Imaging System (LI-COR Biosciences) (Supplementary Fig. 2A). Statistical analysis was carried out using one-way ANOVA and Student t test.
3. Results

We analyzed tau splicing in a cohort of 14 AD cases with (ADTDP+) and 15 AD cases without (ADTDP−) TDP-43 inclusions and 15 age-matched non-demented healthy controls (Supplementary Table 1). The amygdala is consistently affected by tau pathology in AD and, in cases with TDP-43 pathology, the amygdala consistently contains TDP-43 inclusions. In the amygdala, the average molar ratio of isoforms containing or lacking E10 (4R/3R ratio) ranged between 0.7 and 1.2 in control cases. Individually, the ADTDP+ and ADTDP− groups showed a borderline significant increase in the 4R/3R ratio compared to controls (Supplementary Fig. 2B). However, the average 4R/3R ratios were not significantly different between the ADTDP+ and ADTDP− groups.

4. Discussion

Mutations in the TARDBP gene, encoding TDP-43, have been linked to familial forms of amyotrophic lateral sclerosis (Sreedharan et al., 2008), thus arguing for a pathogenic role of TDP-43. Tau premRNA has not been found to be a direct target of TDP-43 (Tollervey et al., 2011). However, TDP-43 is part of an RNA regulatory complex that includes fused in sarcoma (FUS). FUS binds to tau pre-mRNA, and FUS downregulation promotes E10 inclusion in tau mRNA in rodents (Orozco et al., 2012). Whether tau mis-splicing contributes to sporadic AD has been a matter of debate (Niblock and Gallo, 2012). Considering the pathological importance of tau splicing and the role of TDP-43 as a splicing regulator, it was important to determine whether a correlation existed between the presence of TDP-43 pathology in Alzheimer's disease cases, TDP-43 does not critically affect the quality of the material selected. In conclusion, TDP-43 pathological changes in early onset familial and sporadic Alzheimer's disease, late onset Alzheimer's disease and Down's syndrome: association with age, hippocampal sclerosis and clinical phenotype. Acta Neuropathol. 122, 763–773.

Appendix A. Supplementary data

Supplementary data related to this article can be found at the online version at http://dx.doi.org/10.1016/j.neurobiolaging.2015.09.022.

References


