MOLECULAR NEURODEGENERATION

POSTER PRESENTATION Open Access

Analysis of TDP-43 and its binding partners in neurodegenerative diseases

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From Molecular Neurodegeneration: Basic biology and disease pathways
Cannes, France. 10-12 September 2013

Background

Transactive DNA binding protein (TDP-43) is the major component of the ubiquitin-positive protein aggregates seen in ~90% of Amyotrophic Lateral Sclerosis (ALS) and 60% of Frontotemporal Lobar Degeneration (FTLD) cases [1]. We have previously shown that mutations in the gene encoding TDP-43 are causally linked to familial ALS+/-FTLD [2] TDP-43 belongs to the heterogeneous nuclear ribonucleoprotein (hnRNP) family of proteins that are involved in the regulation of RNA transcription, splicing, transport and translation [3]. There are a large number of hnRNPs, many of which have overlapping functions and often act cooperatively in RNA processing. Here we sought to determine whether TDP-43 aggregates contain other hnRNPs that might contribute to the neurodegenerative process.

Materials and methods

Immunohistochemistry for 14 hnRNPs predicted to associate with TDP-43 were examined in brain and spinal cord tissues from 20 FTLD-TDP and ALS cases. Co-localization with TDP-43 was examined using double-labelling immunoflouresence. Expression of selected hnRNPs was then examined in other neurodegenerative cases and controls to determine the specificity of any changes observed.

Results

One hnRNP demonstrated a striking accumulation within dystrophic neurites and cytoplasmic inclusions in the frontal cortex of FTLD-TDP cases. The hnRNP inclusions were not detected in other neurodegenerative cases with mutations of *MAPT*, *FUS*, *SOD1* and *C9ORF72*. This particular hnRNP was found to co-localize with ~85% of TDP-43 inclusions and ~67% of ubiquitin incluions, largely in the frontal cortex and hippocampus of FTLD-TDP cases. Interestingly, the inclusions were not seen in FTLD-TDP cases with C9ORF72 mutation.

Conclusions

We have identified one hnRNP that is abundant within the inclusions seen in FTLD-TDP cases. The hnRNP is seen to colocalize with TDP-43 in the majority of cytoplasmic inclusions in FTLD-TDP but not other neurodegenerative disorders. The mechanistic implications of this interaction with TDP-43 and the contribution of its sequestration into inclusions towards neurodegeneration requires further investigation.

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Published: 13 September 2013

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doi:10.1186/1750-1326-8-S1-P23
Cite this article as: Kattuah *et al.*: Analysis of TDP-43 and its binding partners in neurodegenerative diseases. *Molecular Neurodegeneration* 2013 **8**(Suppl 1):P23.

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