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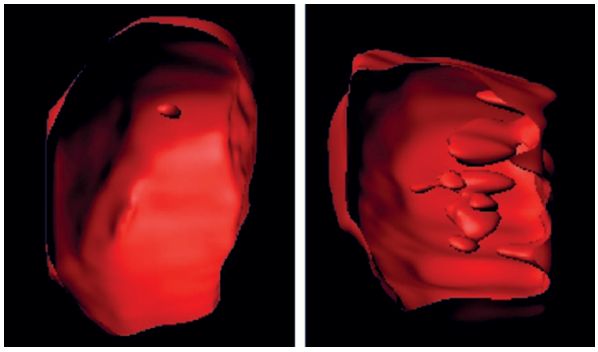
NEURODEGENERATIVE DISEASE

TDP pathology leads to nuclear disruption

> “nucleocytoplasmic transport defects … are likely a common feature of … ALS”

Nucleocytoplasmic transport is disrupted as a result of TAR DNA-binding protein 43 (TDP43) pathology in amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), new research suggests. The findings provide new insight into the pathophysiology of familial and sporadic ALS–FTD, and might reveal a more general mechanistic principle of neurodegenerative disease.

Although mislocalization and aggregation of mutant TDP43 is an established pathological feature of ALS–FTD, the exact contribution of this pathology to neurodegeneration is unclear. To gain insight, Wilfried Rossoll and colleagues analysed TDP43 aggregates to determine which other proteins were present.



In contrast to normal nuclear morphology (left), the nuclear membrane is invaginated in cells that express TDP-CTF (right). Adapted with permission from Macmillan Publishers © Chou, C.-C. et al. *Nat. Neurosci.* https://doi.org/10.1038/s41593-017-0047-3 (2018).

“We hoped to find clues about the disease process and factors that may allow us to prevent disease pathology,” explains Rossoll. “We found many interesting leads, but our first in-depth analysis focuses on the surprising finding that TDP43 aggregates are highly enriched in components of the nucleocytoplasmic transport machinery.” Having identified nucleoporins and transport factors in the aggregates, the researchers went on to examine the functional implications of the mislocalization and aggregation of these proteins.

Co-expression of nucleoporins and transport factors with an aggregation-prone C-terminal fragment of TDP43 (TDP-CTF) in mouse neuroblastoma cells confirmed that some of these proteins co-aggregated with TDP43, whereas others became mislocalized, indicating structural disruption of nuclear pores. Visualization of nuclear morphology also revealed invagination of the nuclear membrane in cells expressing TDP-CTF.

Experiments in mouse primary cortical neurons also showed impairments of nuclear protein import and RNA export in cells that expressed TDP-CTF or mutant TDP43. Similar effects were seen in fibroblasts from a small sample of patients with sporadic ALS, *TARDBP* mutation-associated ALS (TDP-ALS) or *C9ORF72* mutation-associated ALS (C9-ALS).

The findings add to previous work that indicated a role of nucleocytoplasmic transport disruption in C9-ALS. “Our study shows that nucleocytoplasmic transport defects are not only present in C9-ALS but are likely a common feature of the vast majority of ALS cases, including sporadic forms, which are all characterized by TDP43 pathology,” comments Rossoll. “This transport pathway shows an age-dependent decrease in efficiency in neurons, which makes this disease mechanism plausible for a large number of late-onset neurodegenerative disorders, such as Alzheimer disease.”

If the mechanism is found to have a role in other neurodegenerative diseases, Rossoll says, then therapies that are currently in development to target nucleocytoplasmic transport could be more widely applicable than initially thought.

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ORIGINAL ARTICLE Chou, C.-C. et al. TDP-43 pathology disrupts nuclear pore complexes and nucleocytoplasmic transport in ALS/FTD. *Nat. Neurosci.* https://doi.org/10.1038/s41593-017-0047-3 (2018)

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