Neurodegenerative disease

FTD–ALS risk factors converge on the endolysosomal pathway

A diverse range of genetic risk factors have been identified for diseases across the frontotemporal dementia (FTD)–amyotrophic lateral sclerosis (ALS) spectrum, but the underlying cellular and molecular processes that culminate in neurodegeneration are still being unravelled. In a new study published in *Science*, Yong-Jie Zhang, Leonard Petrucelli and colleagues show that variants in two FTD–ALS risk genes — *C9orf72* and *TBK1*, which encodes TANK-binding kinase 1 — impair the functioning of the endolysosomal pathway, leading to pathological intracellular accumulation of TAR DNA-binding protein 43 (TDP43).

"Both G_4C_2 hexanucleotide repeat expansions in *C9orf72* and mutations in *TBK1* are genetic causes of FTD and ALS, and rare patients who co-harbour mutations in both of these genes exhibit an earlier age of onset and a more rapid disease course," explains Petrucelli. "However, how these two disease-related genes connect pathologically is largely unknown, and we wondered whether there is any interplay between these factors in the brain."

The researchers found that expression of *C9orf72* G_4C_2 repeat expansions in the mouse brain, which is known to produce a behavioural and neuropathological phenotype resembling human FTD–ALS, led to increased phosphorylation of TBK1 protein. In cortical cells, the phosphorylated protein was sequestered into puncta and colocalized with poly(GA), a dipeptide repeat protein that is generated through non-AUG translation of G_4C_2 repeats.

"Our study reveals a model in which TBK1 is phosphorylated in response to *C9orf72* poly(GA) aggregation and is sequestered into inclusions, leading to a net decrease in TBK1 activity that contributes to neurodegeneration," comments Zhang. "When TBK1 activity was further reduced by the introduction of the ALS-associated $TBK1^{R228H}$ mutation in mice, poly(GA)-induced phenotypes were exacerbated."

TBK1 sequestration by poly(GA) was also found to be associated with aggregation of TDP43 and accumulation of defective endosomes. These organelles form part of the endolysosomal system and have an important role in protein sorting and trafficking within the cell.

"By uncovering this interplay among *C9orf72*, *TBK1* and TDP43, we have connected three different facets of FTD–ALS into one coherent pathway," concludes Petrucelli. The researchers now plan to investigate whether mutations in other FTD–ALS-linked genes, such as *ALS2*, *FIG4*, *VCP*, *CHPMP2B* and *TMEM106B*, also affect the endolysosomal pathway, and also to further explore the consequences of disrupting this pathway.

Heather Wood

Original article: Shao, W. et al. Two FTD–ALS genes converge on the endosomal pathway to induce TDP-43 pathology and neurodegeneration. *Science* **378**, 94–99 (2022)

Related article: Balendra, R. & Isaacs, A. M. *C9orf72*-mediated ALS and FTD: multiple pathways to disease. *Nat. Rev. Neurol.* **14**, 544–558 (2018)

In brief

COVID-19

Preventing COVID-19 neurological complications

Neurological complications are reported in approximately 4% of people with severe COVID-19. New data reveal that treatment with dexamethasone or remdesivir during acute COVID-19 is associated with a reduced frequency of neurological complications, including stroke, seizures and meningitis. Importantly, the drugs showed a synergistic effect when used together. Moreover, dexamethasone treatment was associated with a decreased risk of neurological complications in individuals with non-hypoxic COVID-19.

Original article: Grundmann, A. et al. Fewer COVID-19 neurological complications with dexamethasone and remdesivir. *Ann. Neurol.* https://doi.org/10.1002/ana.26536 (2022)

Neurodegenerative disease

NUMB72 — a therapeutic target for tauopathies?

A new study has identified the trafficking adaptor protein NUMB as a key regulator of intracellular tau levels. In mouse neurons, overexpression of the NUMB72 isoform decreased intracellular tau and reduced axonal blebbing. Viral vector-mediated delivery of NUMB72 prevented retinal ganglion cell loss and improved visual function in both TauP301S and 3×Tg tauopathy mouse models compared with a control vector. These findings highlight the potential of NUMB72 as a therapeutic target for tauopathies.

Original article: Lacomme, M. et al. Numb regulates Tau levels and prevents neurodegeneration in tauopathy mouse models. *Sci. Adv.* https://doi.org/10.1126/sciadv.abm4295 (2022)

Parkinson disease

Novel plasma markers for Parkinson disease

In an attempt to identify biomarkers for Parkinson disease (PD), researchers have assessed known plasma markers of neuronal function, inflammation and cardiovascular risk in 109 people with PD and 96 healthy matched controls. The results revealed 25 proteins that were differentially expressed in PD, which were validated in an independent cohort. A number of markers correlated with cognitive decline and motor deterioration at follow-up, demonstrating their utility for monitoring disease progression. The findings also offer insight into pathological pathways of PD and identify potential therapeutic targets.

Original article: Bartl, M. et al. Blood markers of inflammation, neurodegeneration, and cardiovascular risk in early Parkinson's disease. *Mov. Disord.* https://doi.org/10.1002/mds.29257 (2022)

Traumatic brain injury

Blood–brain barrier dysfunction following TBI

A new pilot investigation demonstrates the use of dynamic contrast-enhanced (DCE) MRI for characterization of blood–brain barrier (BBB) dysfunction resulting from traumatic brain injury (TBI). DCE MRI in 40 adults with TBI revealed a higher mean volume transfer constant and normalized permeability index value, compared with healthy controls, indicative of BBB disruption in the TBI group. As expected, focal lesions were associated with the greatest BBB disruption, followed by perilesional and nonlesional regions, which showed subtle but still significant elevation of the mean volume transfer constant compared with controls.

Original article: Ware, J. B. et al. Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury. *Neuroimage Clin.* https://doi.org/10.1016/j.nicl.2022.103236 (2022)