Neurodegenerative disease

TDP43 blocks misprocessing of *STMN2* RNA

Nuclear depletion and cytoplasmic accumulation of TAR DNA-binding protein 43 (TDP43) in neurons is a pathological hallmark of various neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia. A study published in *Science* provides new mechanistic insights into the role of TDP43 in regulating the expression of stathmin 2, which is encoded by the *STMN2* gene and is required for axonal regeneration after injury.

"*STMN2* is normally one of the most abundant RNA transcripts in human spinal motor neurons, and we previously discovered that it was the RNA most profoundly lost following mutation or suppression of TDP43," explains co-corresponding author Don Cleveland. "Further inspection revealed that TDP43 dysfunction was triggering truncation of the *STMN2* RNA through the usage of cryptic splicing and premature polyadenylation sites."

The *STMN2* gene contains a cryptic exon known as exon 2a that is not usually incorporated into the mature *STMN2* mRNA. Aberrant splicing of this exon into *STMN2* mRNA truncates the full-length message and introduces a stop codon, thereby preventing production of functional stathmin 2 protein.

In the new study, Cleveland, Michael Baughn, Ze'ev Melamed, Clotilde Lagier-Tourenne and colleagues found that TDP43 binds to a GU-rich region in intron 1 of the *STMN2* pre-mRNA and sterically blocks recognition of cryptic splice and polyadenylation sites by RNA processing factors. Loss of TDP43 allows these factors to access the site, resulting in the splicing of exon 2a into the *STMN2* mRNA.

"The finding that governance of normal *STMN2* pre-mRNA processing by TDP43 is mediated principally through steric binding suggests that this mechanism is druggable with designer DNA drugs," says Cleveland. "Antisense oligonucleotides (ASOs) have been successfully utilized to correct RNA in similar disease contexts such as spinal muscular atrophy."

The researchers generated ASOs that targeted and prevented the use of the cryptic sequences in *STMN2*. These ASOs restored stathmin 2 expression and axonal regeneration capacity in TDP43-deficient neurons. In addition, the ASOs restored normal stathmin 2 RNA and protein levels in mice that were genetically engineered to misprocess *Stmn2* pre-mRNAs.

> **"TDP43 … sterically blocks recognition of cryptic splice and polyadenylation sites by RNA processing factors"**

"Our team eagerly anticipates the publication of our parallel line of investigation, demonstrating the functional consequences of stathmin 2 loss from the adult mammalian CNS, which produces a progressive ALS-like motor phenotype," comments Cleveland. "We are also collaborating with multiple teams to devise new mouse models of TDP43 dysfunction to further explore the consequences of TDP43-dependent misprocessing of *STMN2* RNA."

Heather Wood

Original article: Baughn, M. W. et al. Mechanism of *STMN2* cryptic splice-polyadenylation and its correction for TDP-43 proteinopathies. *Science* **379**, 1140–1149 (2023)

In brief

Parkinson disease

Ultrasound lets gene therapy into the brain

Delivery of gene therapies across the blood–brain barrier (BBB) is a major challenge. In a new study, researchers used low-intensity focused ultrasound to temporarily open the BBB at specific locations in non-human primates and in individuals with Parkinson disease. The process was generally well tolerated and did not result in abnormalities detectable with MRI. In the non-human primates, the researchers administered a green fluorescent protein (GFP)-expressing viral vector intravenously following the ultrasound. GFP was detected post mortem in targeted brain regions, indicating that the approach could facilitate delivery of gene therapies.

Original article: Blesa, J. et al. BBB opening with focused ultrasound in nonhuman primates and Parkinson's disease patients: targeted AAV vector delivery and PET imaging. *Sci. Adv.* **9**, eadf4888 (2023)

Neuroinflammation

Cytomegalovirus link to concussion changes

Cytomegalovirus (CMV) is a neurotrophic virus that is reactivated by stress and inflammation. A new study investigated whether concussion can reactivate CMV, causing damage to the brain. The study included 88 athletes who underwent MRI at various time points following concussion and a control group who underwent a similar imaging schedule. CMV seropositivity was associated with altered cortical thickness and changes to some diffusion tensor parameters, but only in the individuals who had experienced concussion, suggesting that the virus contributes to structural abnormalities after concussion.

Original article: Savitz, J. et al. The effects of cytomegalovirus on brain structure following sport-related concussion. *Brain* https://doi.org/10.1093/brain/awad126 (2023)

COVID-19

Olfactory network function altered in COVID-19

Olfactory dysfunction is common among individuals with COVID-19; however, the pathophysiology underlying this symptom is not yet clear. In a new study, researchers performed brain MRI in individuals with persistent COVID-19-related olfactory dysfunction and a group of healthy control participants. Gross morphological measures did not differ between the two groups; however, graph analysis of the functional olfactory network showed altered connectivity in the individuals with COVID-19. The researchers highlight the need for further studies with larger sample sizes to confirm their findings.

Original article: Muccioli, L. et al. Cognitive and functional connectivity impairment in post-COVID-19 olfactory dysfunction. *Neuroimage Clin.* https://doi.org/10.1016/j.nicl.2023.103410 (2023)

Epilepsy

New blood biomarker of refractory epilepsy

Measuring levels of fucosyltransferase 8 (FUT8) in blood can aid epilepsy diagnosis and prognosis, according to new findings. Researchers measured serum FUT8 levels in 199 individuals with epilepsy, 59 individuals with refractory epilepsy and 22 healthy individuals. The participants were followed up for 2 years. FUT8 levels were significantly higher in individuals with refractory epilepsy than in healthy individuals. Furthermore, in individuals with refractory epilepsy, higher FUT8 levels were associated with a greater likelihood of seizure recurrence, indicating that it could be useful for predicting disease course.

Original article: Huang, Y. et al. Diagnosis and prognosis of serum Fut8 for epilepsy and refractory epilepsy in children. *PLoS ONE* https://doi.org/10.1371/journal.pone.0284239 (2023)