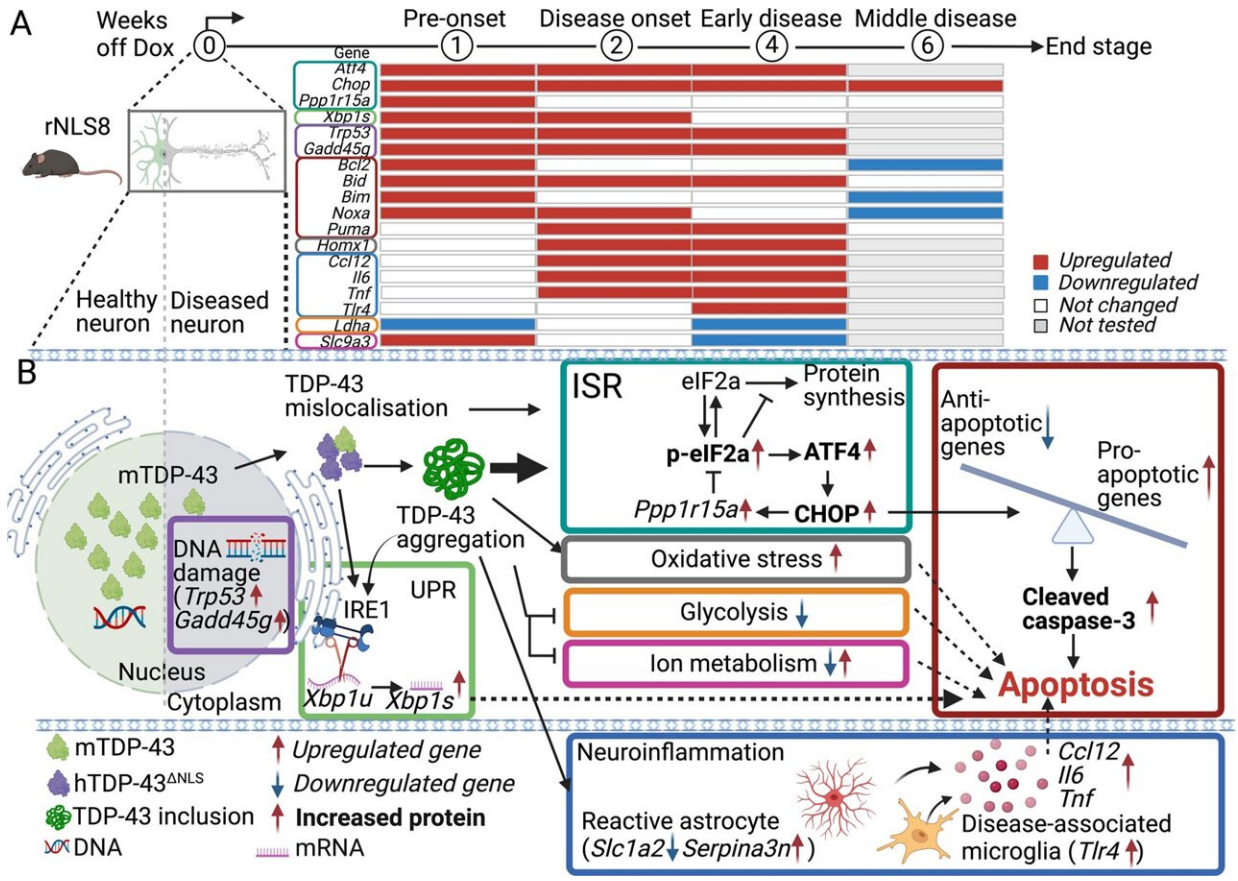
Motor neuron disease treatments a step closer

April 27 2023



TDP-43 pathology causes early activation of the ISR and apoptosis signaling in rNLS8 mice. A Summary of gene expression changes in the cortex of rNLS8 mice over time. B Mechanism schema. TDP-43 mislocalisation induces early activation of multiple cell stress signaling pathways in the cortex of rNLS8 mice even before disease onset, such as the ISR, UPR, DNA damage response, and apoptosis. Notably, the prolonged activation of these cell stress pathways caused by TDP-43 pathology, in particular the ISR, continues through early-disease

stages where rNLS8 mice displayed dramatic elevation of p-eIF2α and ATF4 protein, and impairment of cellular metabolism. Dysregulation of stress pathways leads to reduction of anti-apoptotic Bcl2, continued increased expression of pro-apoptotic genes (Bid, Bim, Noxa, and Puma), and increases of cleaved caspase-3 and astrogliosis, likely contributing to neurodegeneration in rNLS8 mice. Credit: *Molecular Psychiatry* (2023). DOI: 10.1038/s41380-023-02036-9

Research at the University of Queensland could eventually help develop viable treatments—and ultimately a cure—for motor neuron disease (MND).

Dr. Adam Walker and co-authors Dr. Rebecca San Gil, Dr. Wei Luan and Ph.D. student Sean Keating from the Queensland Brain Institute have identified biochemical changes in a protein that is affected by MND. Their research has been published in *Molecular Psychiatry* and *Cellular and Molecular Life Sciences*.

"TDP-43 is a protein found in every cell of the body but is particularly important for the health of motor neurons, the brain cells that control voluntary muscle movement," Dr. Walker said.

"We ran two research projects, looking at how TDP-43 proteins become dysfunctional in motor neurons.

"We found diseased versions of TDP-43 can damage healthy versions of the protein, which may create a cycle of protein dysfunction and degeneration over time.

"We also discovered that biochemical pathways which control neuron death are triggered early, even before MND symptoms begin.

"To change the course of the disease we need pharmaceutical drugs that can prevent neuron death and this TDP-43 protein dysfunction."

The research used genetic engineering technology called CRISPR, which is a gene editing tool.

"It allowed us to see TDP-43 in live cells for the first time," Dr. Walker said.

Co-author Sean Keating said the research also found neural pathways change as MND progresses, indicating the potential need for different treatments at different phases of the disease.

"We are now treating genetically modified mice with MND with different pharmaceutical drugs that specifically target the underlying causes of the disease, and correct the disease mechanism," Mr. Keating said.

"Our aim is to stop the TDP-43 degenerative cycle and halt the progression of the disease.

"This research improves our understanding of MND, and we hope it will play an important role in the fight against the disease."

More information: Wei Luan et al, Early activation of cellular stress and death pathways caused by cytoplasmic TDP-43 in the rNLS8 mouse model of ALS and FTD, *Molecular Psychiatry* (2023). DOI: 10.1038/s41380-023-02036-9

Sean S. Keating et al, Aggregation-prone TDP-43 sequesters and drives pathological transitions of free nuclear TDP-43, *Cellular and Molecular Life Sciences* (2023). DOI: 10.1007/s00018-023-04739-2

Provided by University of Queensland