Investigational drug stops toxic proteins tied to neurodegenerative diseases

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An investigational drug that targets an instigator of the TDP-43 protein, a well-known hallmark of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), may reduce the protein's buildup and neurological decline associated with these disorders, suggests a pre-clinical study from researchers at Penn Medicine and Mayo Clinic. Results were published in *Science Translational Medicine*.

The work shows, for the first time, how toxic poly(GR) (glycine-arginine repeat) proteins produced by the mutated C9orf72 gene stimulate the clumping of TDP-43 found in ALS, also known as Lou Gehrig's disease, and FTD patients. In a mouse model, the researchers also show that treatment with a pipeline drug known as an antisense oligonucleotide (ASO) reduced the levels of poly(GR), TDP-43 clumps, and neurodegeneration along with it.

"A common genetic cause of ALS and FTD is a repeat expansion in the C9orf72 gene, which somehow leads to TDP-43 aggregation in degenerating neurons, but what remained unclear until now was how those two were connected," said co-senior author James Shorter, Ph.D., a professor of Biochemistry and Biophysics in the Perelman School of Medicine at the University of Pennsylvania. "We found that TDP-43 aggregates much more rapidly if these toxic poly(GR) proteins are around, suggesting a direct link between the mutation, poly(GR), and TDP-43."

ALS is the progressive degeneration of motor neurons that control people's muscles, speech, and ability to breathe. FTD, the most common form of dementia in people under 60, results in damage to the anterior temporal and/or frontal lobes of the brain; as it progresses, it becomes increasingly difficult for people to function and even care for oneself.

"This finding presents an exciting potential therapeutic target to treat these debilitating diseases by lowering poly(GR) levels," added Hana Odeh, Ph.D., a post-doctoral fellow in the Shorter lab and co-first author.

After researchers in the Shorter lab demonstrated the role of poly(GR) proteins in TDP-43 accumulation at the protein level, their colleagues at Mayo Clinic in Jacksonville, Fla., studied the interactions in both human cells and mice to support the initial bench side finding at Penn. Co-senior authors from Mayo Clinic include Yongjie Zhang, Ph.D., an assistant professor of Neuroscience, and Leonard Petrucelli, Ph.D., Ralph B. and Ruth K. Abrams Professor of Neuroscience at Mayo Clinic College of Medicine and Science.

They showed in a series of complementary experiments, including immunofluorescence staining and immuno-electron microscopy, that poly(GR) in human cells alone can sequester TDP-43 proteins, and in doing so induce the formation of dense protein clumps. This same mechanism was then demonstrated in a mouse model.

It's worth noting, the researchers said, that the burden of both TDP-43 and poly(GR) correlate with neurodegeneration in patients observed in past studies: the higher the protein levels, the worse the neurological function, providing further evidence that the two proteins are conspiring.

Next, the team delivered an ASO drug known as c9ASO, which is being investigated in clinical trials, into the brains of three-month old mice expressing the ALS/FTD-causing repeat-expansion and found that it had diminished the levels of both poly(GR) and TDP-43 aggregates. c9ASO has been shown to switch off the repeat expansions in the C9orf72 gene and reduce poly(GR), but this is the first time it's been shown to reduce TDP-43 clumping.

To assess the drug's neuroprotective ability, the researchers examined the amount of neurons and plasma neurofilament light (NFL), a known biomarker of neurodegeneration in patients, in treated mice. The drug prevented the reduction of cortical neurons and decreased levels of plasma NFL, they found, suggesting the drug helped confer neuroprotection. "If that extends to patients, the plasma NFL level provides a way to track how effective your therapeutic is," Odeh said.

The researchers plan to study in more detail how TDP-43 and poly(GR) and other similar toxic proteins associated with the mutated C9orf72 interact, and conduct further studies with ASO drugs to better understand their role in stopping the clumping of TDP-43.

"This exciting collaborative study sets the stage for continued teamwork in this space, which I see as being of great interest to the ALS and FTD community," Shorter said.

More information: Casey N. Cook et al. C9orf72 poly(GR) aggregation induces TDP-43 proteinopathy, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.abb3774

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