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Researchers find new link between neurodegenerative diseases and abnormal immune responses

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Researchers from McMaster University and the Icahn School of Medicine at Mount Sinai, New York have discovered that a protein associated with neurodegenerative diseases like ALS also plays an important role in the body's natural antiviral response.

The study, published today in *Nature Immunology*, offers new insight into the link between neurodegenerative disorders and inflammation, and provides a framework to explore more fully the possibility that viral infection may lead to onset of these diseases.

Matthew Miller, an investigator at the Michael G. DeGroote Institute for Infectious Diseases Research, is the study's lead author. He said mutations in the senataxin gene (SETX) are known to cause certain types of neurodegenerative disorders such as amyotrophic lateral sclerosis type 4 (ALS4 - a type of Lou Gehrig's Disease) and ataxia with oculomotor apraxia type 2 (AOA2). However, no one currently understands why these mutations result in neurodegenerative diseases.

"We have found that senataxin deficiency, and cells from individuals with these neurodegenerative diseases, respond abnormally to viral infections," said Miller. "Specifically, they generate abnormally high amounts of inflammation, which is known to play an important role in several neurological diseases. Our study identifies abnormal inflammation as a potential contributing factor in ALS, which opens the

door to explore new therapeutic options."

The scientists studied senataxin, a protein implicated in a juvenile-onset form of amyotrophic lateral sclerosis (ALS) and in ataxia with oculomotor apraxia. ALS, more commonly known as Lou Gehrig's disease, is a rare neurodegenerative condition that affects motor neurons and causes progressive muscle wasting and movement problems. Ataxia with oculomotor apraxia is a rare disorder with an average onset age of 15 that causes muscle control problems and loss of peripheral vision.

The scientists used gene expression studies as well as in-depth chromatin analysis to uncover the regulatory role of the protein. While most previous work to characterize the protein has been conducted in yeast cells, this project gained new information by analyzing human cells as well. The team found that senataxin has far more power to regulate gene activity than was previously known.

Using cutting-edge genomic tools, the researchers found that senataxin is deployed to regulate the body's natural antiviral response at a specific point. Without it, exposure to viral pathogens can lead to inflammation and potentially to life-threatening conditions. People with senataxin-related forms of ALS and ataxia have a defective SETX gene that leads to a dysfunctional form of the protein.

"This is the first protein implicated in neurodegenerative disease that has been linked to our innate antiviral mechanism, and it offers an intriguing clue to the inflammatory response associated with these diseases," said Ivan Marazzi, co-author of the paper and an assistant professor in the Department of Microbiology at Mount Sinai.

"Whether viral infection plays a role in disease progression remains to be seen, but this discovery has broad implications for biomedical research and opens up new avenues that we look forward to pursuing."

More information: Senataxin suppresses the antiviral transcriptional response and controls viral biogenesis, DOI: 10.1038/ni.3132