MedicalXpress

Researchers reveal unusual chemistry of protein with role in neurodegenerative disorders

July 27 2017, by Elise Lamar

A common feature of neurodegenerative diseases is the formation of permanent tangles of insoluble proteins in cells. The beta-amyloid plaques found in people with Alzheimer's disease and the inclusion bodies in motor neurons in the brains of people with amyotrophic lateral sclerosis are two examples. Those aggregates, and others like them, can kill cells and lead to debilitating and progressive neurodegenerative diseases.

A study by Douglas Black and colleagues in UCLA's department of microbiology, immunology and molecular genetics, reveals that not all protein aggregates in brain cells are toxic. Their paper, published in the journal *Cell*, reports that an RNA-binding protein called Rbfox1, which is abundant in the brain, undergoes an unusual chemical transformation to form nontoxic aggregates inside neurons, and that this aggregation is needed for Rbfox1 to perform its essential function, which is splicing RNA during the gene expression process.

Mutations in the Rbfox1 gene are linked with some forms of familial epilepsy and autism spectrum disorder, so scientists are interested in understanding how Rbfox1 controls splicing in the brain. The new discovery is also important because the biochemistry of Rbfox1 is similar to those of proteins that are believed to play roles in several neurodegenerative disorders, including a protein called FUS, which aggregates in amyotrophic lateral sclerosis, also known as ALS or Lou

Gehrig's disease.

In people with ALS, FUS is found in highly stable aggregates that are harmful to cellular function. Understanding what drives the normal aggregation of these proteins could help scientists explain how the toxic aggregates are formed in ALS.

Black's team previously reported that Rbfox1 proteins function with a larger group of proteins called LASR, which together bind to RNA molecules in cell nuclei and direct them to cut and rejoin, a process called mRNA splicing.

"Our new work reveals that in some cases Rbfox must also interact with itself to control splicing," Black said.

Provided by University of California, Los Angeles