Model demonstrates how RNA splicing defects contribute to Alzheimer's disease

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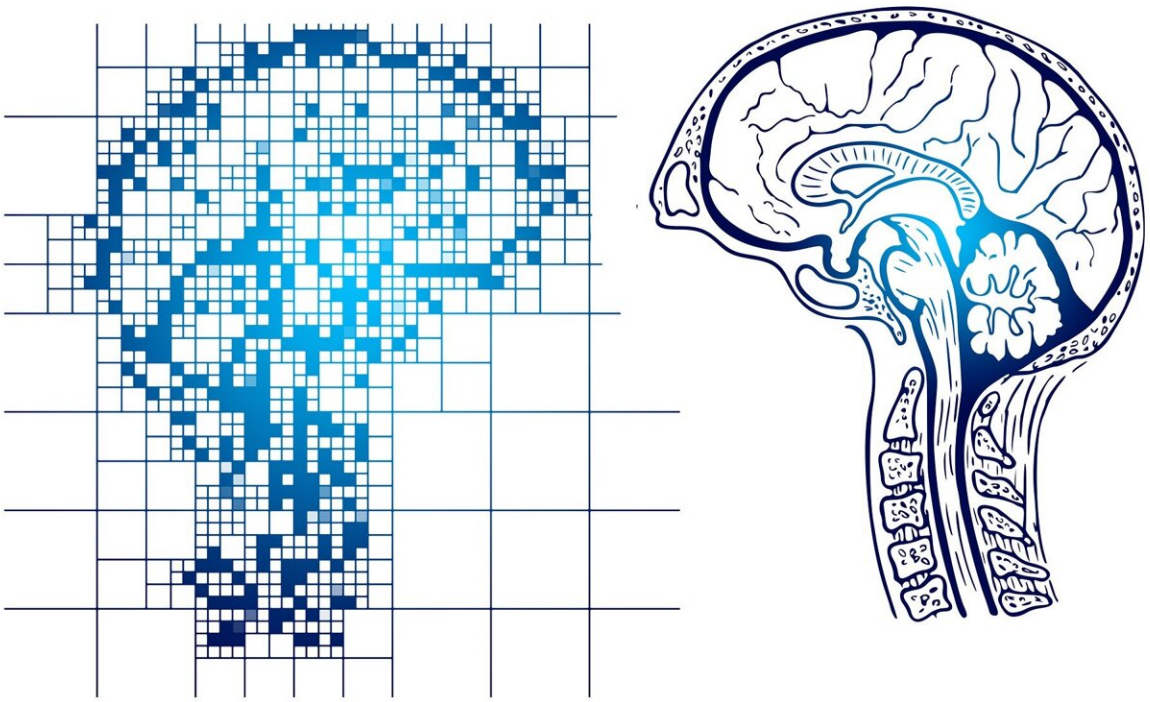

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Researchers have puzzled over the neurodegenerative disorder Alzheimer's disease for decades, but treatments to stop or reverse the disease's effects on the brain have remained elusive. Scientists at St.

Jude Children's Research Hospital recently added an important piece to the puzzle by creating a mouse model that more closely resembles the disease in humans than previous models. The findings appeared today in *Nature Aging*.

The researchers used their new model to discover how defects in RNA splicing contribute to neurodegeneration in Alzheimer's disease. RNA splicing is a process that removes non-coding genetic sequences and joins protein-coding sequences together.

"RNA splicing is an essential step in transcription and translation," said corresponding author Junmin Peng, Ph.D., St. Jude Departments of Structural Biology and Developmental Neurobiology and the Center for Proteomics and Metabolomics, who led the research. "It is particularly important in the brain because we know the brain has more cellular diversity than any other organ in the body and splicing is believed to be an important process for generating protein diversity."

Previous work by Peng revealed that a specific component of the RNA splicing machinery, called the U1 small nuclear ribonucleoprotein (snRNP), creates aggregates in the brains of individuals with Alzheimer's. The U1 snRNP complex is essential in RNA splicing.

Now, Peng and his team have demonstrated that the dysfunction of the U1 snRNP contributes to neurodegeneration, opening new avenues of research for Alzheimer's treatment. The study found that RNA splicing dysfunction due to U1 snRNP pathology helps cause neurodegeneration.

"Our previous work showed that the U1 snRNP is a type of aggregate in the brain that forms tangle-like structures—but that is just descriptive, we didn't understand the mechanisms that link this pathology to the disease phenotype until now," Peng said.

Unique model links RNA splicing defects with neuronal hyper-excitability

The researchers created a novel mouse model of RNA splicing defects called N40K-Tg. The scientists observed basic neurodegeneration when they deregulated the splicing machinery, but they wanted to understand why that was the case.

"Splicing machinery is so essential, and creating a model to study it in the lab was a real challenge," Peng said. "We were able to create a model of splicing dysfunction that occurred only in neurons. This model demonstrates splicing dysfunction that causes neuronal toxicity as well as cognitive impairment."

Inhibitory neuron activity prevents the brain from getting over-excited. If a scientist represses the inhibitory neuron activity, the neurons become more active, but it can cause toxicity. The researchers found a significant impact on synaptic proteins, in particular the proteins involved in inhibitory neuron activity.

"Excitatory toxicity is very important because it is already known in the Alzheimer's disease field," Peng said. "Even 20–30 years ago, people recognized that neurons become super excited, and now we find that the splicing machinery may be contributing to the excitatory toxicity observed in Alzheimer's patients."

RNA splicing defects and β-amyloid aggregation combined

One hallmark of Alzheimer's disease is the presence of aggregates of β-amyloid and tau in the brain. Peng's previous work revealed that U1 snRNP forms aggregates in the brain as well, but scientists were unable

to study the role of the U1 snRNP function in disease until they developed a model that perturbed U1 snRNP function causing RNA splicing defects.

To understand how the RNA splicing defects behave in the context of β-amyloid aggregation, the researchers crossed their mouse model with one for β-amyloid. Together, the two types of toxic insults remodel the brain's transcriptome and proteome, deregulate synaptic proteins and accelerate cognitive decline.

"From the initial behavior to the cell biology and now to the molecular mechanism, we've characterized the potential contribution of RNA splicing machinery to neuron excitatory toxicity in Alzheimer's disease," Peng said.

This crossed mouse model more closely resembles Alzheimer's in humans than earlier models and may be useful for future research on the disease.

More information: Ping-Chung Chen et al, Alzheimer's disease-associated U1 snRNP splicing dysfunction causes neuronal hyperexcitability and cognitive impairment, *Nature Aging* (2022). DOI: 10.1038/s43587-022-00290-0

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