Q&A: What role does alternative splicing play in neurodegenerative disease?

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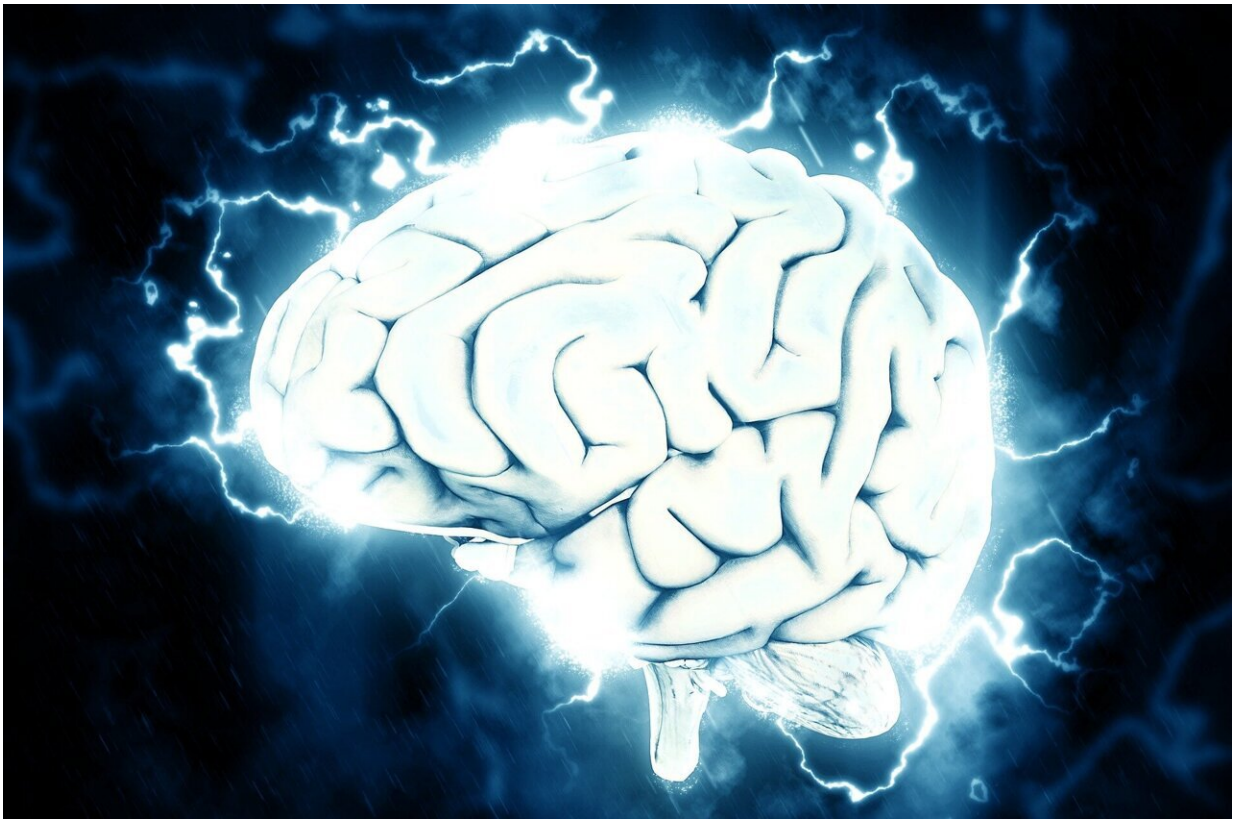

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Alternative splicing, a clever way a cell generates many different variations of messenger RNAs—single-stranded RNAs involved in protein synthesis—and proteins from the same stretch of DNA, plays an

important role in molecular biology. Progressing rapidly, the field of alternative splicing is a complex topic and the scientific literature on it is already extensive.

David Nikom, a student in the UC Riverside Neuroscience Graduate Program, and his advisor, Sika Zheng, an associate professor of biomedical sciences in the UCR School of Medicine and director of the Center for RNA Biology and Medicine, have written a review in *Nature Reviews Neuroscience* to discuss emerging research and evidence of the roles of alternative splicing defects in major neurodegenerative diseases. They also summarize the latest advances in RNA-based therapeutic strategies to target these disorders.

According to them, the topic of alternative splicing in neurodegenerative disease is particularly relevant in view of the increasing frequency of neurodegenerative disease worldwide and the urgent need for novel approaches for their treatment and management. They argue that since aberrant splicing dysregulation occurs commonly in neurodegenerative disease, the promise of using RNA therapies is important to understand and well-suited for a review.

Titled "Alternative Splicing in Neurodegenerative Disease and the Promise of RNA Therapies," their review aims at providing comprehensive, all-inclusive knowledge for a scientific audience interested in the topic. It synthesizes knowledge and discoveries from decades of research made by many labs worldwide on Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS, frontal temporal dementia, etc. In the following Q&A, Zheng and Nikom unpack key aspects of the review.

What is alternative splicing dysregulation?

Once the DNA of a gene is transcribed into a pre-messenger RNA (RNA

before it is spliced), only a small fraction of the pre-messenger RNA makes into the final messenger RNA, or mRNA, transcript that encodes protein. Alternative splicing is a process by which a cell can select which of those protein-coding parts to include in the resulting RNA or protein. Alternative splicing dysregulation is when this process goes wrong in some way. The cell chooses to include the wrong protein-coding parts or exclude some correct parts. This can cause all sorts of problems with the resulting protein: it could be shorter than it is supposed to be which would disrupt its normal function in the cell, or it could result in the protein not being produced at all.

What role does alternative splicing play in molecular biology?

Alternative splicing greatly expands the diversity of the proteins that can be made from a single gene. This is important because multicellular organisms make so many different types of cells that compose the diverse tissue types of their body. But each cell only has the same genetic code. To produce the dazzling complexity of multicellular life, cells depend on alternative splicing to give them the flexibility to make large families of similar proteins with different tissue-specific and developmental stage-specific functions. For example, certain alternative splicing networks are only activated during embryonic development and get shut down when the organism matures.

Briefly, how does it contribute to the molecular pathology of a wide range of neurodegenerative diseases?

Certain organs rely on alternative splicing to generate cellular diversity more than others. We don't know why for sure, but the brain has more alternative splicing going on than any other organ in the body. Scientists

speculate this might be due to the brain's unique complexity, rapid evolution, or the extraordinary diversity of cell types it contains. What we do know is that there are a lot of brain-specific alternative splicing events that consistently go wrong in neurological diseases.

These include neurodevelopmental disorders, like autism spectrum disorder, or neurodegenerative diseases, like Alzheimer's Disease or ALS. The best understood example we have so far has to do with dysregulated alternative splicing in ALS. Scientists found these erroneous splicing events lead to production of aberrant proteins or reduction of normal proteins, which ultimately affect neuronal health and function. Some other neurodegenerative diseases with dysregulated alternative splicing include frontotemporal dementia, Parkinson's disease, Familial dysautonomia, Huntington's disease, spinal muscular atrophy, and Duchenne muscular dystrophy.

Does alternative splicing play a role in other diseases?

Alternative splicing has been linked to about 15% of human genetic diseases and cancers. Mutations in the components that regulate alternative splicing are causative for many diseases, both common and rare. Myotonic dystrophy, myelodysplastic syndromes (bone marrow cancers), retinal degenerative disorders like retinitis pigmentosa, and progeria (rare premature aging syndrome) are prominent examples of diseases caused by splicing defects.

You conclude the review with the latest advances in RNA-based therapeutic strategies developed to target the underlying splicing mechanisms. What are some of these advances?

A good example of targeting underlying splicing mechanisms to treat

diseases is with a disease called spinal muscular atrophy, a major genetic disease of children and infants. Humans carry two near identical copies of the Survival Motor Neuron gene: SMN1 and SMN2 which are essential for the survival of all animal cells. Patients with Spinal Muscular Atrophy have loss of SMN1; SMN2 is the only source of the SMN protein in patients.

The critical difference between SMN1 and SMN2 is splicing of exon 7, a small fragment of protein-coding sequence within the SMN gene. Unlike SMN1 exon 7, SMN2 exon 7 is usually not included in most tissues. The exon 7-skipped transcript generated by SMN2 produces a partially functional and unstable protein. The first therapeutic approval for SMA targets the SMN2 pre-mRNA and binds to a region that is accessed by the splicing machinery to remove exon 7.

This ultimately leads to blocking of the removal of exon 7 and promotes the formation of functional SMN protein. By promoting splicing of exon 7, this drug (Spinraza) increased SMN expression in the cell from the SMN2 gene, compensating for the loss of SMN1, and preventing the loss of cells in the central nervous system.

This story is a textbook example of a splicing mechanism that can be targeted to treat an otherwise fatal disease in children. The hope is to understand many more splicing mechanisms and find new ways to target them to treat other diseases.

Some of the latest advances:

- Splice-switching oligonucleotides (like Spinraza) for tauopathies—neurodegenerative disorders with abnormal tau protein deposition—that can correct the balance of disease-causing isoforms (tau-RNA variants) in the brain
- Splice-splicing oligonucleotides targeting amyloid proteins that

can reduce brain plaques in Alzheimer's mice
- Spliceosome-mediated RNA trans-splicing (SMaRT)—gene reprogramming system designed to correct aberrantly spliced mRNAs by replacing the entire coding sequence upstream or downstream of a splice site
- RNA-targeted CRISPR approaches that can reverse splicing defects without altering the patient's genome like traditional gene therapies.

More information: David Nikom et al, Alternative splicing in neurodegenerative disease and the promise of RNA therapies, *Nature Reviews Neuroscience* (2023). DOI: 10.1038/s41583-023-00717-6

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