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Targeting upper motor neurons to treat ALS

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Scientists have demonstrated for the first time that it is possible to specifically modify gene expression in diseased upper motor neurons, brain cells that break down in ALS.

The new Northwestern Medicine study, published in *Nature Gene Therapy*, provides evidence that lays a foundation for developing future gene replacement therapies to treat patients with the fatal neuromuscular disorder.

Using a nontoxic virus injected directly into the motor cortex of mouse models with ALS, the scientists showed they can deliver new genes to damaged upper motor neurons. This process of transferring DNA from a virus to neurons is called transduction.

To test the feasibility of transduction, the research team had the virus deliver a gene that expresses a green fluorescent protein - the color helped the scientists visualize how the neurons worked. Now that they know the transduction strategy is effective, they'll use it in future research to deliver genes that correct mutations in ALS cells.

Importantly, the scientists were able to specifically modify the gene expression in diseased upper motor neurons without disturbing other neurons in the motor cortex. Inadvertently manipulating other cells could set off a cascade of unknown effects.

"The brain is very complex, with many different cells, but in ALS only a distinct neuron population shows initial vulnerability and undergoes

progressive degeneration," said lead study author Hande Ozdinler, assistant professor of neurology at Northwestern University Feinberg School of Medicine. "To develop effective treatment strategies, we must deliver genes only to the neurons in need. This is not easy to accomplish - previous studies have managed to induce a broad but non-specific transduction of many different neurons."

ALS, or amyotrophic lateral sclerosis, is marked by the deterioration of motor neurons, which causes muscle weakness and impaired speaking, swallowing and breathing, eventually leading to paralysis and death. In previous research, Ozdinler showed that defects in upper motor neurons (also known as corticospinal motor neurons), which send messages from the brain to the spinal cord to activate voluntary movement, may be a starting point for the disease.

In the recent study, Ozdinler's team tested seven different strains of the adeno-associated virus. They found that a nontoxic strain called AAV2-2, already used in clinical studies for diseases such as Parkinson's, was able to deliver genes to damaged upper motor neurons at rates higher than ever seen before.

"With just a one-time injection into the motor cortex, genes were very specifically delivered to the upper motor neurons," Ozdinler said. "Among all cells transduced, about 70 percent were upper motor neurons. Without selectivity, this would be about 1 percent."

The investigators showed that the AAV2-2 virus transduced upper motor neurons in models of both pre-symptomatic and symptomatic stages of ALS, suggesting patients could eventually benefit from therapy based on this work even after they've started experiencing symptoms.

"This new study has very important clinical implications, especially for patients with familial ALS who display upper motor neuron defects,"

Ozdinler said.

An upper motor neuron projects information to the spinal cord through its axon, a long, branch-like part of the cell that sends impulses to other cells. The fluorescent protein that was transferred to the neurons made this process visible.

"We saw that during ALS, damaged upper motor neurons stop talking to spinal neurons," Ozdinler said. "In further research, we will examine how we can modulate gene expression to introduce correct versions of mutated genes and improve that connectivity and motor functions."

Provided by Northwestern University