MedicalXpress

Removing protein 'garbage' in nerve cells may help control two neurodegenerative diseases

December 20 2012

Neuroscientists at Georgetown University Medical Center say they have new evidence that challenges scientific dogma involving two fatal neurodegenerative diseases—amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD)—and, in the process, have uncovered a possible therapeutic target as a novel strategy to treat both disorders.

The study, posted online today in the Journal of Biological Chemistry, found that the issue in both diseases is the inability of the cell's protein garbage disposal system to "pull out" and destroy TDP-43, a powerful, sometimes mutated gene that produces excess amounts of protein inside the nucleus of a nerve cell, or neuron.

"This finding suggests that if we're able to 'rev up' that clearance machinery and help the cell get rid of the bad actors, it could possibly reduce or slow the development of ALS and FTD," says the study's lead investigator, neuroscientist Charbel E-H Moussa, MB, PhD. "The potential of such an advance is very exciting." He cautions, though, that determining if this strategy is possible in humans could take many years and will involve teams of researchers.

The way to rev up protein disposal is to add parkin—the cell's natural disposal units—to brain cells. In this study, Moussa and his colleagues demonstrated in two animal experiments that delivering parkin genes to neurons slowed down ALS pathologies linked to TDP-43."

Moussa says that his study further demonstrates that clumps known as "inclusions" of TDP-43 protein found inside neuron bodies in both disorders do not promote these diseases, as some researchers have argued.

What happens in both diseases is that this protein, which is a potent regulator of thousands of genes, leaves the nucleus and collects inside the gel-like cytoplasm of the neuron. In ALS, also known as Lou Gehrig's disease, this occurs in motor neurons, affecting movement; in FTD, it occurs in the frontal lobe of the brain, leading to dementia.

"In both diseases, TDP-43 is over-expressed or mutated, and the scientific debate has been whether loss of TDP-43 in the nucleus or gain of TDP-43 in the cytoplasm is the problem," Moussa says.

"Our study suggests TDP-43 in the cell cytoplasm is deposited there in order to eventually be destroyed—without contributing to disease—and that TDP-43 in the nucleus is causing the damage," he says. "Because so much protein is being produced, the cell can't keep up with removing these toxic particles in the nucleus and the dumping of them in the cytoplasm. There may be a way to fix this problem."

Moussa has long studied parkin, a molecule best known, when mutated and inactive, for its role in a familial form of Parkinson's disease. He has studied it in Alzheimer's disease and other forms of dementia. His hypothesis, which he has demonstrated in several recently published studies, is that parkin could help remove the toxic fragments of amyloid beta protein that builds up in the brains of Alzheimer's disease patients.

What's more, he developed a method to clear this amyloid beta when it begins to build up in neurons—a gene therapy strategy he has shown works in rodents. Work continues on this potential therapy.

In this study, Moussa found that parkin "tags" TDP-43 protein in the nucleus with a molecule that takes it from the nucleus and into the cytoplasm of the cell. "This is good. If TDP-43 is in the cytoplasm, it will prevent further nuclear damage and deregulation of genetic materials that determine protein identity," he says.

"This discovery challenges the dogma that accumulation of TDP-43 in the cytoplasm is," Moussa says. "We think parkin is tagging proteins in the nucleus for destruction, but there just isn't enough parkin around—compared with over-production of TDP-43—to do the job."

Moussa says his next research steps will be to inject a drug that activates parkin to see whether that can prolong the lifespan and reduce motor defects in mice with ALS.

Provided by Georgetown University Medical Center