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Boosting protein garbage disposal in brain cells protects mice from Alzheimer's disease

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Gene therapy that boosts the ability of brain cells to gobble up toxic proteins prevents development of Alzheimer's disease in mice that are predestined to develop it, report researchers at Georgetown University Medical Center. They say the treatment – which is given just once - could potentially do the same in people at the beginning stages of the disease.

The study, published online in *Human Molecular Genetics*, demonstrates that giving brain cells extra parkin genes promotes efficient and effective removal of amyloid particles believed to be destroying the neurons from the inside. This revved up protein disposal process prevents the cells from dying and spewing amyloid proteins into the brain, where they stick together and clump into plaque, they say.

"At its core, this is a simple garbage in-garbage out therapy, and we are the first to show that this gene attacks amyloid beta inside brain cells for degradation," says the study's lead investigator, neuroscientist Charbel E-H Moussa, M.B., Ph.D.

He adds that the strategy may work for other brain disorders. "Many neurodegenerative diseases are characterized by a toxic build-up of one protein or another, and this approach is designed to prevent that process early-on," he says.

The novelty of Moussa's work is that he believes diseases like Alzheimer's starts when neurons are unable to get rid of toxic amyloid

beta that begins to build up inside neurons – an idea that he says remains controversial, but is rapidly gaining acceptance among neuroscientists.

Moussa has documented a connection between Alzheimer's, Parkinsonism (such as Dementia with Lewy Bodies, or DLB), and Down's syndrome, finding that what these disorders have in common is a build-up of amyloid beta. In Parkinsonism, or secondary Parkinson's disease, the toxic protein may be found in Lewy bodies, which are clumps of protein that clogs the brain of people with DLB, and in some people with Parkinson's disease. People with Down's syndrome produce too much amyloid protein because they have three copies of the chromosome (21) that generates amyloid. "They have dementia because they have too much amyloid in their brains," Moussa says.

He and his colleagues developed a unique model system that mimics the early stages of these diseases. They used a lentivirus, a modified, inert form of HIV, to deliver amyloid beta into the motor cortex of rats, and showed that this produced a buildup of amyloid beta inside neurons, but not an accumulation outside of the cells. They hypothesize that once the stockpile of amyloid beta inside the cell reaches a critical level, neurons burst, and the amyloid beta proteins begin to stick together in the space between brain cells, forming plaque.

Additionally, tau pathology is triggered by amyloid beta inside neurons, causing tau malfunctions, and the whole process results in increased brain inflammation.

So what Moussa and his team tested was removal of the amyloid beta buildup inside neurons. In earlier studies, they used the same model gene delivery system to express extra parkin in the brain of rats at the same time they received amyloid beta. Parkin is part of the ubiquitin ligase complex of proteins that helps target other proteins for degradation inside of the cell, and mutations in parkin are known to cause an early

onset familial form of Parkinson's disease. In the earlier studies, the researchers found that in rats that had received amyloid beta, parkin effectively cleared the protein away.

In this study, they used triple transgenic mice that are often used as a model of human Alzheimer's disease. They develop intracellular amyloid beta at six months of age and extracellular amyloid beta plaque about 3-6 months later.

The researchers injected parkin in one side of the brain of young mice, and left the other side untouched, as a control to compare effects of the treatment.

They found that providing brain cells with about 50 percent more parkin protein activates two parallel garbage-removal processes within the brain. One is ubiquitination, in which errant proteins are targeted for destruction and recycling within the cell. The other process is autophagy, in which membranes form around damaged mitochondria (the cell's power plants) and these membranes fuse with lysosomes that destroys the contents. This is particularly important, Moussa says, because damaged mitochondria have been found to clog the insides of neurons affected by Alzheimer's disease, and the extra parkin seems to help clear them. That allows the cells to produce new and healthy mitochondria.

"With a normal amount of parkin, the cells are overwhelmed and cannot remove molecular debris. Extra parkin cleans everything," Moussa says.

In a second experiment, the research team found that mice given parkin genes through the lentiviral vector had 75 percent less amyloid beta plaque in their brains, compared to mice that were not treated, and that neuronal cell death was also reduced by that amount. They also showed that parkin cleared away so much amyloid beta inside cells that the function of normal glutamate neurotransmission in the hippocampus was

restored. This is especially important, the authors say, because glutamate is key to memory formation, retention and retrieval. "Hypothetically, these damaged cells could restart memory formation," Moussa says.

Moussa says the research team has done all the animal work necessary for an application to begin studying the treatment in humans, starting with an analysis of safety.

He adds that if these experiments are successful, the goal will be to use the treatment as early as possible in the course of a neurodegenerative disease. "Our hope is to stop the whole process early on, but if it is later, perhaps we can halt progression," he says.

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