Sorting protein in neurons defends against neurodegenerative disease

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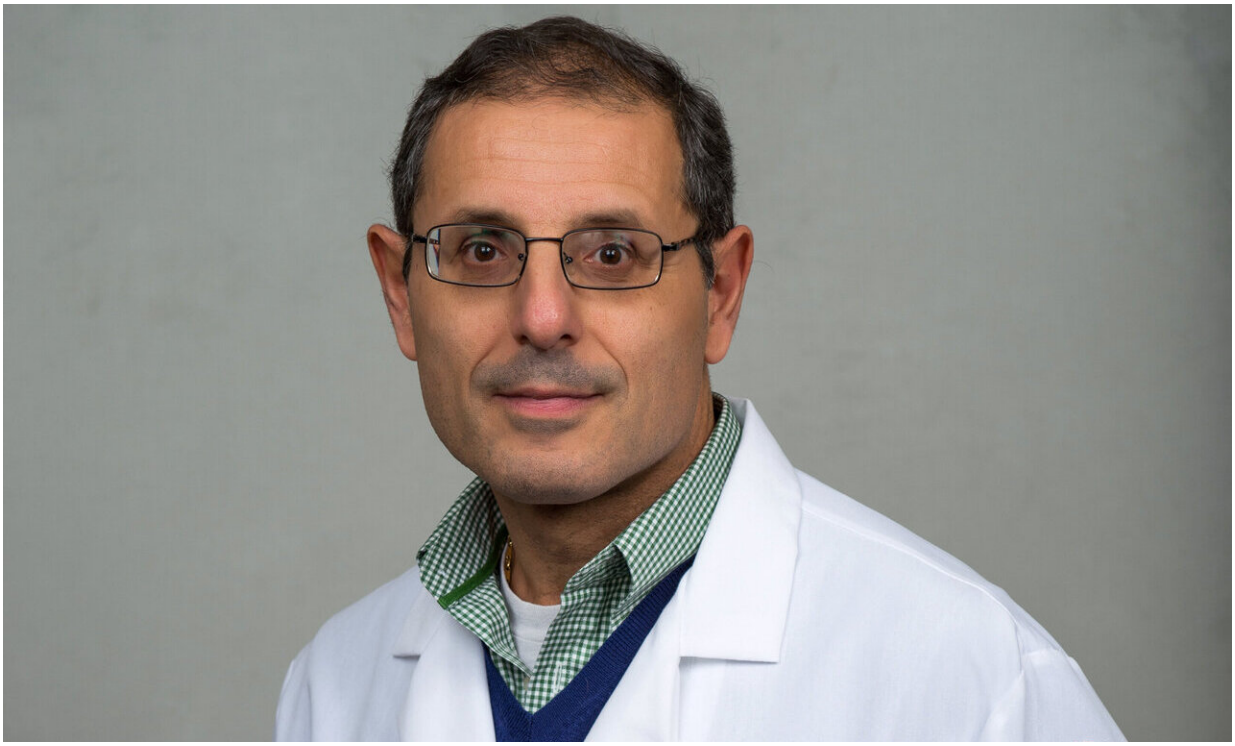

Domenico Praticò, MD, Scott Richards North Star Foundation Chair for Alzheimer's Research, Professor in the Departments of Pharmacology and Microbiology, and Director of the Alzheimer's Center at Temple at the Lewis Katz School of Medicine at Temple University Credit: Lewis Katz School of Medicine at Temple University

Like a sorting machine in an assembly line, a molecule known as VPS35

detects and removes defective proteins from neurons. And similar to other quality control processes, the VPS35 system goes a long way toward protecting health, according to new work by researchers at the Lewis Katz School of Medicine at Temple University. They show for the first time that VPS35 clears the brain of a potentially harmful protein called tau, which otherwise accumulates and contributes to neurodegenerative disorders, including Alzheimer's disease.

The new findings were published online July 9 in the journal *Molecular Psychiatry*.

"A major part of what VPS35 does is to sort out and transport dysfunctional proteins to degradation sites," explained senior investigator Domenico Praticò, MD, Scott Richards North Star Foundation Chair for Alzheimer's Research, Professor in the Departments of Pharmacology and Microbiology, and Director of the Alzheimer's Center at Temple at the Lewis Katz School of Medicine (LKSOM).

The buildup of defective proteins in neurons is a feature shared by Alzheimer's disease, Parkinson's disease, and several other neurodegenerative conditions. Tau is one of the major proteins to amass in the brain and cause damage in these diseases, creating a condition described as tauopathy.

Previous work by other researchers had shown that the function of VPS35 is altered in Alzheimer's disease and that VPS35 activity is reduced in the brains of Alzheimer's patients. The relationship between VPS35 activity and tau accumulation was largely unexplored.

"We asked specifically whether the VPS35 system is important for clearing defective tau proteins," Dr. Praticò said. To answer this question, his team of researchers examined brain tissue from patients with either progressive supra-nuclear palsy (PSP) or Picks' disease.

Unlike Alzheimer's disease, in which tau accumulation is secondary to that of beta-amyloid, in PSP and Picks' disease tau is the only protein to form deposits in the brain.

Analyses revealed that the brains of PSP and Pick's disease patients had VPS35 levels that were 50 percent lower than those of control subjects. When the researchers deliberately altered VPS35 levels in individual tauopathy-affected neurons in vitro, they discovered that they could directly control tau accumulation, for the first time implicating VPS35 in tauopathy. The VPS35-dependent effect on tau was mediated by the activity of cathepsin D, an enzyme that specializes in protein degradation.

Dr. Praticò's team also carried out experiments in mice with tau accumulation. VPS35 downregulation in these animals exacerbated memory and learning impairment and was associated with worsened motor function. Moreover, VPS35 reduction resulted in a loss of synaptic integrity between neurons in the animals' brains, significantly damaging neural communication.

"When tau lingers in cells, it is very bad for synapses, the places where neurons meet and exchange signals," explained Dr. Praticò. "In the animals we studied, there was a 40 to 50 percent loss in synaptic connectivity when VPS35 activity was reduced, which led to the types of cognitive and motor deterioration, including losses in memory and learning ability, seen in human tauopathy patients."

The discovery of the involvement of cathepsin D shed additional light on the relationship between VPS35 and tau. "Without VPS35, cathepsin D does not degrade tau, leaving tau to build up in the brain," Dr. Praticò said.

Dr. Praticò's team plans next to investigate the possibility of using a drug

to put VPS35 back to work in the context of neurodegenerative disease. "The approach would be unique. Instead of targeting an enzyme, as other small molecules have been developed to do, we would be targeting an actual mechanism, which should be more viable," he said.

Provided by Temple University

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