Scientists uncover major factor in development of Huntington's disease

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have uncovered a major contributor to Huntington's disease, a devastating progressive neurological condition that produces involuntary movements, emotional disturbance and cognitive impairment.

Using an animal model of Huntington's disease, the new study shows that signaling by a specific protein can trigger onset of the disease and lead to exacerbation of symptoms. These findings, published in the October 28, 2014 issue of the journal *Science Signaling*, offer a novel target for drug development.

It has been more than 20 years since scientists discovered that mutations in the gene *huntingtin* cause Huntington's disease; the product of the gene, Huntingtin protein, is widely expressed is almost all of the cells in the body.

The disease results in an early loss of neurons in the striatum, part of the forebrain that is responsible for coordinating thought with movement—when you want to move your arm, the striatum lets your muscles know. Unfortunately, the precise physiological role for huntingtin in disease onset and progression remains unclear.

The new study, however, shows for the first time a functional connection between huntingtin and mTOR, a developmentally important gene that integrates signals from multiple pathways, such as growth factors and hormones, to regulate a variety of critical cell functions. Specifically, the scientists found that the huntingtin protein activates signaling by a protein complex known as mTORC1 (mechanistic-target of rapamycin kinase (mTOR) complex 1). Depleting huntingtin reduces mTORC1 activity; an overexpression of huntingtin increases it.

"In our previous work, we showed that there is a protein in the striatum that interacts with huntingtin and makes it more toxic—this protein can activate mTORC1," said Srinivasa Subramaniam, a TSRI biologist who led the study. "What we didn't know was how TORC1 and huntingtin were related. What we found for the first time in this new study is that huntingtin can activate mTORC1 and increase its activity in the striatum of mice—thus prematurely initiating the disease."

In the new research, Subramaniam and his colleagues selectively deleted a gene that inhibits mTORC1 activity in the animal model striatum, which caused a relatively rapid increase in the severity of behavioral abnormalities related to Huntington's disease, as well as premature death.

"This indicates for the first time that huntingtin is a novel regulator of mTORC1 activity that contributes to the pathogenesis of the disease, at least in animal models," he said.

The researchers will continue to investigate the role of mTORC1 in Huntington's and other age-dependent neurodegenerative diseases.

"We think that huntingtin may regulate mTORC1 both in the brain and in other tissue," said William Pryor, the first author of the study and a member of Subramaniam's laboratory. "Our suspicion is that this exacerbation of mTORC1 might compromise autophagy—the pathway that recycles proteins and organelles—which has been implicated in neurodegeneration."

"Reducing mTORC1 activation either through drugs or low-protein foods may have a positive influence on preventing the disease process," said Subramaniam.

In addition to Subramaniam and Pryor, other authors of the study, "Huntingtin Regulates mTORC1 Pathway that Exacerbates Huntington Disease Pathogenesis," include Neelam Shahani, Supriya Swarnkar, Wen-Chin Huang and Damon T.

Page of TSRI; and Marta Biagioli and Marcy E. MacDonald of the Center for Human Genetic Research, Massachusetts General Hospital.

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