Study shows for first time how Huntington's disease protein could cause death of neurons

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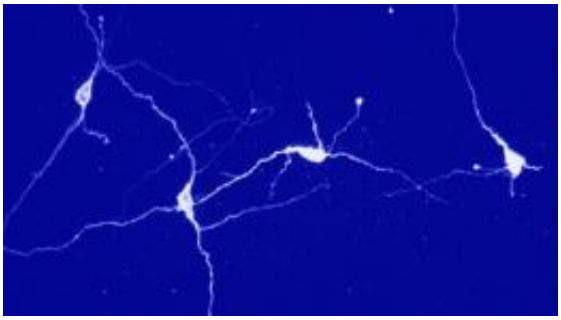

Neurons. Image credit: Denis Burdakov

(Medical Xpress)—Scientists at the University of Pittsburgh School of Medicine have identified for the first time a key molecular mechanism by which the abnormal protein found in Huntington's disease can cause brain cell death. The results of these studies, published today in *Nature Neuroscience*, could one day lead to ways to prevent the progressive neurological deterioration that characterizes the condition.

Huntington's disease patients inherit from a parent a gene that contains too many repeats of a certain DNA sequence, which results in the production of an abnormal form of a protein called huntingtin (HTT), explained senior investigator Robert Friedlander, M.D., UPMC Professor of Neurosurgery and Neurobiology and chair, Department of Neurological Surgery, Pitt School of Medicine. But until now, studies have not suggested how HTT could cause disease.

"This study connects the dots for the first time and shows how huntingtin can cause problems for the mitochondria that lead to the death of neurons," Dr. Friedlander said. "If we can disrupt the pathway, we may be able to identify new treatments for this devastating disease."

Examination of brain tissue samples from both mice and human patients affected by Huntington's disease showed that mutant HTT collects in the mitochondria, which are the energy suppliers of the cell. Using several biochemical approaches in follow-up mouse studies, the research team identified the mitochondrial proteins that bind to mutant HTT, noting its particular affinity for TIM23, a protein complex that transports other proteins from the rest of the cell into the mitochondria.

Further investigation revealed that mutant HTT inhibited TIM23's ability to transport proteins across the mitochondrial membrane, slowing metabolic activity and ultimately triggering cell-suicide pathways. The team also found that mutant HTT-induced mitochondrial dysfunction occurred more often near the synapses, or junctions, of neurons, likely impairing the neuron's ability to communicate or signal its neighbors.

To verify the findings, the researchers showed that producing more TIM23 could overcome the protein transport deficiency and prevent cell death.

"We learned also that these events occur very early in the disease process, not as the result of some other mutant HTT-induced changes," Dr. Friedlander said. "This means that if we can find ways to intervene at this point, we may be able to prevent neurological damage."

The team's next steps include identifying exact binding sites and agents that can influence the interactions of HTT and TIM23.

More information: Astrocyte Kir4.1 ion channel deficits contribute to

neuronal dysfunction in Huntington's disease model mice, *Nature Neuroscience* 17, 694–703 (2014) DOI: 10.1038/nn.3691