3 brain diseases linked by toxic form of same neural protein

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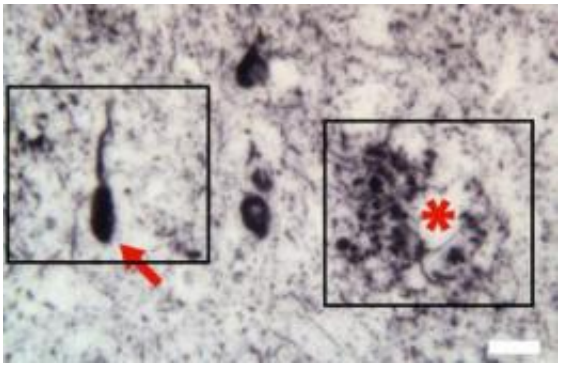

The toxic form of Elk-1 is present in plaque found in brain tissue from an Alzheimer disease patient (red asterisk). A neuronal process of a dying neuron is denoted by the red arrow. Credit: James Eberwine, PhD, University of Pennsylvania School of Medicine

For the first time, researchers from the University of Pennsylvania School of Medicine have found that three different degenerative brain disorders are linked by a toxic form of the same protein. The protein, called Elk-1, was found in clumps of misshaped proteins that are the hallmarks of Parkinson's disease, Alzheimer's disease, and Huntington's disease.

"These results suggest a molecular link between the presence of inclusions and neuronal loss that is shared across a spectrum of neurodegenerative disease," notes senior author, James Eberwine, PhD,

co-director of the Penn Genome Frontiers Institute and the Elmer Holmes Bobst Professor of Pharmacology. "Identifying these links within the diseased microenvironment will open up novel avenues for therapeutic intervention. For example it is reasonable to now ask "Is this molecule a possible new biomarker for these neurodegenerative diseases ?" says Eberwine.

Eberwine, co-first authors Anup Sharma, an MD-PhD student, Jai-Yoon Sul, PhD, Assistant Professor of Pharmacology, both from Penn, Linda M. Callahan, PhD, from the University of Rochester Medical Center, and colleagues, report their findings this week in the online journal PLoS One.

Neurodegenerative diseases are characterized by a number of features including the protein clumps called inclusions; decline of nerve-cell synapses; and the selective loss of the nerve cells themselves.

Elk-1 resides within multiple brain areas, both in the nucleus and the cell body. Interestingly, when it is present in extensions of nerve cells called dendrites, it can initiate the death of that neuron. With this in mind the team assessed whether there is a specific dendrite form of Elk-1 or a modified form called phospho-Elk-1 (pElk-1) that might be associated with a spectrum of human neurodegenerative diseases.

First, they determined the importance of this specific modification of Elk-1 on its ability to initiate regionalized cell death. This was accomplished through site-directed mutations and insertion of the mutated Elk-1 mRNA into dendrites and cell bodies. These studies showed that a specific position on the protein could be modified in the dendrite to cause neuronal cell death.

Next, they screened tissue from a post-mortem human brain bank, specifically samples representative of the three major neurodegenerative

diseases, to look for higher levels of the toxic form of Elk-1 protein and compared their findings to levels in brain tissue from age-matched control samples.

By comparing the immunoreactivity for the pElk-1 protein in diseased tissue versus control tissue, they found that pElk-1 strongly associates with the pathological markers present in cases of Parkinson's disease, Alzheimer's disease, and Huntington's disease versus disease-free tissue.

The team hopes to next expand these preliminary findings to a larger sample size of tissues from neurodegenerative disease banks, and to screen blood samples from affected individuals to assess the biomarker capacity of this form of Elk-1 and to use animal models of these illnesses to assess the biological role of this modified form of Elk-1 in the disease processes. They also will be looking for other sites of toxic changes on the Elk-1 protein and will look in other disease tissue for modified Elk-1.

Provided by University of Pennsylvania School of Medicine