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Protein Linked to Movement Disorders

Using a tiny worm to model a severe childhood movement disorder, researchers at The University of Alabama have discovered the role of a protein that may have implications for a number of neurological syndromes such as Parkinson's and Huntington's diseases.

With support from grants from the Howard Hughes Medical Institute and the Dystonia Medical Research Foundation, the scientists found that a mutated gene associated with early onset dystonia, a severe hereditary movement disorder, normally helps manage protein folding.

The mutated gene, *TORIA* (or *DYT1*), was linked to the disorder in 1997, but the role of its protein, torsinA, had been unknown until this finding, reported in the cover article of the February 1, 2003, issue of *Human Molecular Genetics*.

"We believe that torsinA and the family of torsin proteins are normally neuroprotective, used by cells as a quality control mechanism to clear proteins that have misfolded," said the lead author of the article, Guy Caldwell, assistant professor of biological sciences.

"When torsin's protective mechanism goes awry, it results in protein aggregation, which could be a cause of neuron malfunction," he said.

Caldwell and colleagues were able to provide the first molecular explanation of torsinA's function by using the microscopic nematode roundworm *Caenorhabditis elegans* (*C. elegans*), an animal model that has aided in deciphering cellular functions for genes involved in neuronal functioning. Almost half of all human hereditary diseases, including dystonia and Parkinson's disease, have been linked to genetic components also found in *C. elegans*, according to Caldwell.

While early onset dystonia is rare and characterized by twisting contortions, muscle contractions, or abnormal postures that begin in childhood, dystonia diseases are the third most common movement disorders.

"Dystonia is possibly a consequence of the inability of neurons to properly respond to environmental or physiological stress-induced changes in protein structure," Caldwell said. "Specific changes in torsin activity may render cells more susceptible to such stresses."

These findings further suggest that malfunctioning torsin proteins may play a role in a number of diseases that feature abnormal aggregations of protein. For example, torsin has been found in protein clumps known as Lewy bodies in the brains of patients with Parkinson's disease, Caldwell said.

"Failure of proteins to adopt their proper structure is a common cause of neuronal dysfunction, and many diseases of the nervous system involve aggregates, or clumps, of protein forming in cells," he explained.

The researchers transplanted the green fluorescent protein (GFP) that causes jellyfish to glow into *C elegans* and induced it to form misfolded protein aggregates. Introducing functioning torsinA into the worm significantly reduced the fluorescent protein clumps, whereas worms genetically altered to produce a mutated form of torsin similar to that associated with dystonia were unable to suppress the formation of protein clumps. "Torsin activity appears to be conserved across species, from humans to worms," Caldwell said.

This successful experimental technique opens the door to a number of new investigative avenues, the scientists say. Their lab has already genetically engineered a fusion between GFP and a human protein, alpha-synuclein, implicated in Parkinson's disease, and early findings show "torsins are equally effective in suppressing alpha-synuclein aggregation in worms," Caldwell said.

The work also raises the question of whether torsins might be useful as a therapeutic drug to prevent protein clumping, the researchers say. "There is a potential for torsins as molecules that serve a more general neuroprotective function in preventing misfolding of proteins within cells," Caldwell said. "They may have promise as a novel class of therapeutics for diseases in which misfolded protein aggregates are suspected to be a causative factor, such as Parkinson's, Alzheimer's, spinocerebellar ataxias, and Huntington's."

The study's co-authors are all members of Caldwell's lab. They include Kim Caldwell, Songsong Cao, Elaina Sexton, Christopher Gelwix, and John Paul Bevel. The lab recently was named one of 11 worldwide to receive a research grant from the Michael J. Fox Foundation for Parkinson's Research.