SOUTHWESTERN NEWS

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'Vicious cycle' of protein formation involved in Parkinson's disease

DALLAS – June 21, 2005 – Researchers at UT Southwestern Medical Center have discovered a mechanism that causes a protein to clump together in brain cells of people with Parkinson's disease, pointing toward a possible treatment for the condition.

The protein clumping is part of a "vicious cycle," the researchers said. As the proteins cluster, they inhibit an enzyme that normally breaks them down, leading to the formation of even more masses.

"It's a disease involving accumulation of a protein in an aberrant form," said Dr. Philip Thomas, professor of physiology at UT Southwestern and senior author of the study. The research, available online, was published in the June 17 issue of *The Journal of Biological Chemistry*.

The findings have parallels to other diseases in which protein clusters form in and around nerves, such as Huntington's and Alzheimer's disease.

The culprit in Parkinson's is the protein alpha-synuclein, which normally appears in a long, folded form in cells. It's known to be linked to the disease because mutations in it cause rare, inherited cases of early-onset Parkinson's.

Normally, if a cell becomes stressed, alpha-synuclein unfolds, and an enzyme degrades it completely into harmless bits to prevent the clumping. In Parkinson's patients, however, some of the degrading enzyme malfunctions and creates truncated fragments of alpha-synuclein rather than the harmless bits.

UT Southwestern researchers found that these truncated fragments act like "seeds," encouraging the unfolded form of alpha-synuclein to gather around them. It doesn't take much – just a few molecules of the truncated fragments – to activate this process. Eventually, the cluster is big enough to form a structure called a fibril.

The two forms of the enzyme are usually in balance, with the normal activity outperforming the malicious activity, Dr. Thomas said.

But when the system goes out of balance, the fibrils suppress the normally functioning enzyme, preventing it from fully breaking down the unfolded alpha-synuclein, resulting in even more of the

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protein being available to form clumps. The clumps also alter the structure of the enzyme in such a way that it produces even more seed fragments. This leads to the formation of more clumps, and so on.

Scientists are still debating which form of the alpha-synuclein protein actually damages the cells, said Dr. Chang-Wei Liu, research fellow in physiology at UT Southwestern and lead author of the study. It could be the mature fibril, or one of the intermediate forms that appears during the degradation process, he said.

Future research may involve uncovering methods to inhibit just the malicious form of the enzyme, while leaving the functions of the normal enzyme unaffected, Dr. Thomas said. Inhibiting only one form is vital, because the normal enzyme is necessary for cells to survive.

Still, the finding reported in *The Journal of Biological Chemistry* "gives us clues about potential new treatment avenues," he said.

Other UT Southwestern authors of the study are Karen Lewis, student research assistant in physiology, and Dr. George DeMartino, professor of physiology. Researchers at the University of Pennsylvania School of Medicine also contributed.

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