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Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

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Enzyme action creates protein linked to Alzheimer's disease

DALLAS – Aug. 12, 2005 – Researchers at UT Southwestern Medical Center have defined a key step in the production of beta-amyloid, a short protein that is thought to be responsible for the development of Alzheimer's disease. Understanding this step may aid in the discovery of drugs that could help block the disease from developing.

In Alzheimer's disease, too much beta-amyloid is produced by an enzyme that has many other essential roles. As a result, simply blocking the whole enzyme knocks out many of its other functions – which is fatal to the organism.

Using cultured human and mouse cells, as well as test-tube assays, UT Southwestern researchers singled out how just one portion of the enzyme, a protein called nicastrin, is involved in the pathway that produces beta-amyloid, thereby leading to Alzheimer's disease. They hope next to work on ways to specifically block nicastrin. The study appears in the August 12 issue of the journal *Cell.*

"The work provides an attractive potential strategy for developing treatment for Alzheimer's disease," said Dr. Gang Yu, assistant professor in the Center for Basic Neuroscience and of cell biology and senior author of the study. The research uncovered an "unprecedented mechanism of biochemistry," Dr. Yu said.

Nicastrin is a large protein that is a component of an enzyme called gamma-secretase, which is lodged in the cell's membrane. When it is at the cell surface, nicastrin sticks out into the area outside the cell. It has been thought to play a key role in the creation of a protein called amyloid-beta – the prime suspect for the damage Alzheimer's does to the brain – but the exact mechanism was unknown.

Dr. Yu and his colleagues found that nicastrin binds to several proteins lodged in the cell's membrane, including one called amyloid precursor protein, or APP. Nicastrin then guides membrane-bound proteins to the active area of gamma-secretase, which then splits the proteins. APP, for example, is chopped into two parts: amyloid-beta, which is then shipped to the outside of the cell, and another part that remains inside. Amyloid-beta forms the plaques seen in brains afflicted with Alzheimer's.

"Actually, it's quite a simple mechanism," Dr. Yu said. "Hopefully, we can screen for

(MORE)

compounds that can block this process and find the exact pathways and how it can be regulated in Alzheimer's disease."

Now that nicastrin's function has been ascertained, it opens a way to block just the splitting of APP, leaving all the enzyme's other functions intact. For instance, it may be possible to generate chemical compounds that specifically prevent nicastrin from latching on to APP. If APP doesn't attach to nicastrin, APP remains intact and harmless. Meanwhile, nicastrin would be free to bind all the other essential proteins that it works on.

"We want to find a particular way to block the recognition of APP but not the others," Dr. Yu said.

UT Southwestern researchers in the Center for Basic Neuroscience involved in the study were Sanjiv Shah, lead author and student research assistant; Drs. Sheu-Fen Lee and Katsuhiko Tabuchi, assistant instructors; Drs. Yi-Heng Hao and Cong Yu, postdoctoral researchers; and Dr. Thomas Südhof, director of the center. Other UT Southwestern researchers were Quincey LaPlant, Medical Scientist Training Program student; Dr. Charles E. Dann III, postdoctoral researcher in biochemistry; and Dr. Haydn Ball, assistant professor of biochemistry.

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