

Genetic parsing of precursor protein gives clues to Alzheimer's disease

Baylor College of Medicine
HOUSTON -- (September 29, 2010) -- As researchers try to understand how a particular protein sets the stage for the toxic plaques that wreak havoc on the brains of people with Alzheimer's disease, they face a dilemma. This protein, called the amyloid precursor protein, not only begins the damaging process that results in Alzheimer's, it also has a critical biological function in brain development and in the synapse (the junction between nerve cells or nerve and muscle cells). To figure out how this protein causes Alzheimer's, they must figure out what parts of this precursor protein are necessary for normal development and activity and which contribute to disease.

Pinpointing functions

In a report in the current issue of the [Journal of Biological Chemistry](#) [1], a team led by researchers from [Baylor College of Medicine](#) [2] shows that one end of this membrane-spanning protein, the C-terminus that resides within the cell, plays a critical role in brain and synapse development but not in the formation of the toxic plaques in the brain.

"Tampering with this region of the protein through drug or other treatment might interfere with the normal biological functions of the amyloid precursor protein without affecting the accumulation of plaque in the brain," said Dr. Hongmei Li, a postdoctoral associate in the lab of [Dr. Hui Zheng](#) [3], director of the [Huffington Center on Aging](#) [4] at Baylor College of Medicine. Zheng is the paper's senior author.

Developing drugs

Such information is important in determining how to proceed in developing drugs against Alzheimer's, said Li. There is no cure for Alzheimer's disease and drugs currently approved only slow it down. Alzheimer's disease affects as many as 5.3 million Americans today and its toll will only grow as the population ages. It is now the seventh-leading cause of the death in the United States.

Tackling the problem of developing drugs to slow or cure disease depends on understanding the activity of the proteins involved, said Li.

There are actually three members of the amyloid precursor protein family – APP, APLP1 and APLP2. Mice that lack any one of these proteins are fine, but those that lack APLP2 and one of the other family members die soon after birth. This indicates the importance of the proteins in brain development and that the activities of these

three members of the family overlap to some degree.

Studying C-terminal region

To study the C-terminal region, Li and her colleagues bred a special mouse in which the amyloid precursor protein contained a region called A beta peptide that came from the human form of the protein. The A beta peptide is the major component in the plaques or protein tangles called amyloid plaque found in the brains of people with Alzheimer's disease. Within this region, the mice had three mutations associated with familial forms of Alzheimer's disease. The C-terminal region of the protein in these mice was also mutated.

When these mice were bred with mice that lacked the APLP2 protein, their offspring died soon after birth.

"They also had abnormal formation of the neuromuscular synapse," said Dr. Zilai Wang, also a postdoctoral associate in Zheng's laboratory. His interest lies in the development and function of that neuron-muscular junction.

When the researchers crossed their mice with the human forms of mutations associated with familial Alzheimer's disease with mice that had mutations in a protein called presenilin1, they expected to speed up the disease. Presenilin 1 is part of the protein machinery that cuts the amyloid precursor protein into segments, generating the toxic A beta peptide. The disease occurred earlier in the mice. The researchers found abundant amounts of amyloid plaque in the brains of the offspring, either with or without a functional C-terminus region.

This indicates that the C-terminus region of the amyloid precursor protein, which is mutated in this and other specially bred mice, is important to the proper development of the brain and the synapse, but it has no effect on the disease process, said Qinxi Guo, a graduate student in BCM's Translational Biology and Molecular Medicine program, whose main interest is studying genetic ally engineered mice bearing the mutations causing familial Alzheimer's disease.

N-terminus region

The same team describes an important function of a region called the N-terminus of the amyloid precursor protein. This finding might eventually lead to new approaches in treating Alzheimer's disease. In the Proceedings of the National Academy of Sciences (www.pnas.org [5]), with Li and Dr. Baiping Wang, a research associate in Zheng's laboratory, as co-first authors, the group describes how a region of a soluble form of amyloid precursor protein (the N-terminus region) enhances expression of two genes, transthyretin and Klotho. Transthyretin can bind the A beta peptide and inhibit its aggregation. Klotho appears to have an effect on aging. When there is too much of the protein in mice, they live 20 to 30 percent longer.

Zheng, senior author of the report and the team's mentor, said that this finding

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demonstrates a novel function for amyloid precursor protein that is separate from its role in development of the neuromuscular synapse.

"Our findings raise the possibility that impaired APP (amyloid precursor protein) extracellular processing could contribute to Alzheimer's disease pathogenesis during aging through misregulation of transthyretin and Klotho," said Zheng. Misregulation means that something interferes with the normal function of the gene.

These research projects were initiated and mentored by Dr. Thomas Südhof's when he was at The University of Texas Southwestern School of Medicine in Dallas. After he moved to Stanford University, the projects continued under Zheng's guidance at BCM. Others who took part in this research include Drs. Geogia Dolio and Rong Wang of Mount Sinai School of Medicine in New York, Dr. Katsuhiko Tabuchi and Dr. Robert Hammer of The University of Texas Southwestern School of Medicine in Dallas.

Funding for this work came from the National Institute on Aging of the National Institutes of Health and the American Health Assistance foundation.

The full papers are available:

- [Journal of Biological Chemistry](#) [6]
- [Proceedings of the National Academy of Sciences](#) [7] (Epub Sept. 20, 2010)

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