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Keeping Amyloid—and Alzheimer's—in Check

Researchers have identified a protein that reins in the rogue activity of the molecules that make the amyloid-beta protein—which may prevent normal brain function in people with Alzheimer's disease. Their findings reveal a potentially powerful tool for designing novel Alzheimer's treatments.

Amyloid beta-peptides are sticky, neurotoxic protein fragments that accumulate, kill nerve cells, and clump together to form the distinctive amyloid plaques in the brains of people with Alzheimer's disease. They are generated when a larger, normal protein called amyloid precursor protein (APP) is cleaved or split in a series of events. A protein complex called the presenilin complex is responsible for the final cleavage event.

"Presenilin complexes don't just arbitrarily chop up proteins."

- Peter St George-Hyslop

Presenilin complexes are thought to cause an unusual form of protein cleavage in which selected membrane proteins are split in a region that crosses cell membranes. This previously unrecognized form of protein cleavage is essential for several normal signaling processes. The same presenilin complex also generates amyloid-beta from APP. The presenilin cleavage that generates amyloid-beta may be a physiological process unrelated to signaling. In fact, it may just be a way to remove unneeded protein stubs from cellular membranes.

However, new findings from Howard Hughes Medical Institute (HHMI) international research scholar Peter St George-Hyslop at the University of Toronto argue against this hypothesis. St George-Hyslop's group recently pinpointed a new component called TMP21 that controls presenilin's dicing tendencies, preventing it from snipping apart APP. The researchers report

their findings in the April 27, 2006, issue of the journal *Nature*.

When TMP21 was first discovered, it appeared to be a "cargo transporter" that embeds itself in the membranes of transport vesicles—small, bladder-like sacs that shuttle proteins from one cellular locale to another. St George-Hyslop's group discovered that TMP21 moonlights by performing another distinct and independent role within presenilin complexes.

To understand TMP21's role in presenilin complexes, the researchers removed the protein from cells. What they saw surprised them: amyloid-beta levels nearly doubled. Restoring TMP21 returned amyloid-beta levels to normal.

TMP21 appears to keep amyloid-beta levels in check by preventing the specific cleavage of APP that leads to its production. Remarkably, TMP21 does not affect another cleavage also performed by the presenilin complex, one that generates molecules that relay messages from one nerve cell to another.

“Presenilin complexes don't just arbitrarily chop up proteins,” said St George-Hyslop. “The cleavage events involved in signaling and amyloid-beta formation are separate, discretely regulated processes. These data suggest that the presenilin complexes are likely to be as complex and as important as the proteasome (a complex structure inside the cell that breaks down proteins) in cleaving proteins, as the function of the complex is dependent on key proteins that regulate its activity.”

Identification of TMP21 in presenilin complexes and its role in amyloid-beta formation may change the way researchers design drugs for Alzheimer's treatment. “Many compounds have been generated that block presenilin function, but they block both kinds of cleavage events. Finding a molecule that mimics TMP21 would provide a means of specifically blocking only gamma secretase function,” said St George-Hyslop. A TMP21 mimic could prevent the formation of amyloid-beta fragments while preserving the complex's ability to control communication between nerve cells.

There may be more, still-unidentified proteins that affect the function of the presenilin complex. “Does TMP21 finish off the complex?” said St George-Hyslop. “I don't think so. There are probably some other elements that modulate other functions.” It may also be significant, he added, that the cleavage that produces amyloid-beta occurs at a slightly different location

than the cleavage that generates signaling molecules.

Further investigation of the regulatory proteins controlling presenilin complexes may reveal other potential targets for drugs to treat Alzheimer's disease, which affects as many as 4.5 million Americans and nearly half a million Canadians. Up to now, attempts to develop medicines to inhibit amyloid-beta production have been hindered, the researcher said, because they frequently inhibit the normal and essential signaling functions too.

Michael Glista, a senior at Kalamazoo College in Michigan, worked in St George-Hyslop's laboratory as an HHMI undergraduate researcher during the summer of 2005. He helped develop a technique for purifying TMP21 for use in cell-free experiments. Although Glista's stay was brief, St George-Hyslop welcomed the help of the young man, whom he called "a highly driven and focused student."

Glista, one of 21 undergraduates that HHMI placed in the labs of its international research scholars worldwide in 2005, said he particularly wanted to work in St George-Hyslop's lab because of the importance of Alzheimer's research. "When I explained the work I did to others, a lot of them could really relate to it, which is great positive reinforcement," said Glista.

His biomedical research experience also helped to confirm his desire to pursue an M.D.-Ph.D. degree. "Dr. St George-Hyslop told me that you don't go into research to become famous; you do it because you love it. I think this is really practical advice that rings true for me," said Glista.