Function found for Alzheimer's protein

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In people with Alzheimer's, the brain becomes riddled with clumps of protein, forming what are known as amyloid plaques. Now, a report appearing in the September 17th print issue of *Cell* appears to have found a function for the amyloid precursor protein (APP for short) that yields the prime ingredient in those plaques.

It turns out that APP is an iron oxidase whose job it is to convert iron from an unsafe form to a safe one for transport or storage. When APP fails to function properly, as it does in Alzheimer's disease, iron levels inside neurons mount to toxic levels.

"This opens a big window on Alzheimer's disease and iron metabolism," said Ashley Bush of The Mental Health Research Institute, University of Melbourne.

"Although people have attributed several important physiological roles to APP," added Jack Rogers of Harvard Medical School, "this now gives us an idea of what this critical protein does to underpin its role in iron metabolism."

In fact, there were some clues. Some years ago, the researchers discovered that the RNA template for the APP protein includes an iron-responsive element. When iron levels rise, cells ramp up their APP production.

But amyloid in and of itself doesn't really explain what goes wrong in the Alzheimer's brain. "There has been a lot of attention on amyloid, but it

seems it is not a simple matter of amyloid as the sole culprit," Bush said. For one thing, trials of drugs designed to target and clear amyloid plaques haven't worked as intended.

In fact, the disease is also complicated by high concentrations of metals, including iron that builds up inside neurons and zinc that accumulates within the amyloid plaques outside of those brain cells. And studies have also linked the loss of other iron oxidases to pathological iron accumulation and neurodegenerative diseases characterized by dementia. "If iron is left unbridled in its soluble form, it can cause nerve death and damage," Rogers said.

After 10 years of work, it appears Bush's and Roger's teams have connected the dots from the abnormal exchange of zinc to amyloid pathology and iron accumulation in Alzheimer's disease. "It's a sequence of dominoes falling onto each other," Bush said.

They show that APP is a bona fide iron oxidase, with properties much like the best-known iron oxidase (called ceruloplasmin), which is not expressed in neurons. Loss of APP in cells and primary neurons causes iron levels to build, while increasing APP promotes the export of iron out of cells.

Mice lacking APP become vulnerable to dietary iron, which causes the unsafe, oxidative form of iron to build in the animals' neurons, they show. Finally, they show that zinc in amyloid blocks APP's normal iron-balancing activities in the Alzheimer's brain.

Based on the new evidence, the researchers propose that elevated iron in the Alzheimer's brain summons further APP production. But that APP -- generated for the purpose of exporting iron -- gets disabled by high levels of zinc that dissociate from the amlyoid plaques.

The findings suggest that zinc may be an ideal target in the fight against Alzheimer's disease, the researchers say. In fact, studies in animals and early, short-term clinical trials of zinc-ionophore drugs including clioquinol and PBT2 in people with Alzheimer's disease have so far produced promising results. PBT2 is slated for further testing.

"Our findings authenticate zinc as a target," Bush said. "It really makes it look like an attractive place to hit."

Although Rogers said that he doesn't want to raise hopes for an Alzheimer's cure too high, "this is definitely an important step in getting to a therapy to retard the Alzheimer's disease process."

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