Amyloid-Beta ‘Oligomers’ May Be Link to Alzheimer’s Dementia

by Jim Schnabel

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Much evidence points to the involvement of the protein amyloid-beta (A-beta) in causing Alzheimer’s disease, but researchers increasingly are shifting their suspicions away from the large and insoluble aggregates of A-beta seen in patients’ brains at autopsy or in brain-imaging studies. These “plaques” don’t seem to be a good indicator of the extent of dementia: Some people have many plaques yet seem cognitively normal.

Many researchers now suspect that smaller, still-soluble clusters of A-beta, known as oligomers, are the main source of neuron-harming toxicity in the disease. This hypothesis has been hard to prove, though, in part because there has been no easy way to isolate these oligomers from other forms, or “species” of A-beta in living animals or humans. But separate teams of researchers have just reported that levels of the smallest A-beta oligomers, called dimers, can be measured—and do closely reflect the presence of disease.

“I think it opens the door for us to develop tools so we can specifically identify the A-beta species that could be used as biomarkers for the presence of Alzheimer’s,” says Dominic Walsh, a biochemist at University College Dublin who led one of the research groups.

In the May issue of Brain, Walsh and colleagues reported measuring levels of soluble A-beta proteins in the brains of 43 just-deceased patients in a population-wide sample. They used three common solvent mixtures to process brain tissue, and found that for two of these, the measured level of soluble A-beta in single-protein (“monomer”) form served as a good indicator of disease. The presence of oligomers made of two conjoined A-beta proteins—“dimers”—was an even better indicator: The researchers frequently detected significant levels of the dimers in the brain samples from people with Alzheimer’s type dementia, but almost never in brains from people with non-Alzheimer’s dementia or no dementia.
“To me the results are no surprise,” says Kevin Barnham, whose lab at the University of Melbourne in Australia has been doing similar studies. “Small oligomers of A-beta are clearly a high priority target for diagnostic and therapeutic strategies.”

There is still no consensus about the precise ways by which oligomers harm neurons. One leading hypothesis is that they affect the synapses on neurons that make connections with other neurons, so that it becomes harder for the brain to form new memories and recall old ones, and eventually the affected synapses disappear. A paper in 2008 by a team including Walsh and other members of his present study reported that A-beta dimers isolated from human Alzheimer’s brains could have such “synaptotoxic” effects on the brains of rats.

In the Alzheimer’s disease process, it appears that both the monomers and the dimers of A-beta go on to form larger toxic clusters, until they become insoluble and relatively harmless fibrils that are deposited in plaques. Walsh suspects that the aggregation pathway starting from dimers is more dangerous because “the [larger species] formed from dimers are more resistant to the transition to fibrils,” and thus tend to hang around longer in a toxic form.

**Changing the drug target?**

One implication of such studies is that prospective Alzheimer’s therapies should target A-beta dimers specifically. But most of the A-beta-clearing drugs that have been tested in clinical trials, such as the monoclonal antibody bapineuzumab [see story, “Early Results of Alzheimer’s Passive Vaccine Trial Mixed”], also should clear the dimers—and so far none of those approaches has been proven even to slow the course of Alzheimer’s dementia.

That may be simply because these treatments came too late. “Once a certain amount of damage has been done, it’s really hard to regenerate what’s been lost or even to change the disease course,” says Ganesh Shankar, a neurologist now at Massachusetts General Hospital who participated in the study and was lead author on the 2008 synaptotoxicity paper.

One way to treat Alzheimer’s patients earlier is to diagnose it earlier, and this may be the nearest-term clinical result of this new focus on oligomers. “These soluble A-beta dimers represent a new molecular target” for Alzheimer’s diagnosis, says Shankar.

Since the A-beta dimers of interest are only in the nervous system, researchers normally would expect to measure them in samples of cerebrospinal fluid, taken via a spinal tap. But another recent study by Kevin Barnham and his colleagues suggests that a simple blood test might be feasible. Reporting in the *Journal of Neuroscience* on May 5, the team analyzed blood samples from 118 elderly people. Some had
mild to moderate Alzheimer’s, while others had normal cognitive function or mild cognitive impairment (MCI).

Previous studies had suggested that blood levels of A-beta are not an accurate marker of Alzheimer’s disease status, but those studies hadn’t targeted soluble A-beta oligomers. The earlier studies also had made use of only the plasma or serum fraction of blood, discarding the “cell enriched” (CE) fraction that debris from red and white blood cells.

Since A-beta’s formation and its theorized toxicity occur in and around cell membranes, Barnham and colleagues reasoned that A-beta in blood might bind to the membranes of blood cells, and so might be found at higher levels in the usually-ignored CE fraction. Looking at this part with an advanced form of mass spectrometry to distinguish the sizes of soluble species of A-beta, they found that both monomers and dimers were significantly elevated in the Alzheimer’s patients compared with the cognitively normal controls. A third A-beta species, slightly larger than a dimer, was found to be significantly decreased in the Alzheimer’s patients. These correspondences also held up when the levels of these three species were compared with patients’ results on other Alzheimer’s diagnostic tests, such as cognitive tests and measures of brain shrinkage.

“As far as we are aware this is the first time such clinically relevant tests have been correlated with a biomarker found in peripheral tissue,” Barnham says. “It raises the possibility that disease status is reflected in blood biochemistry.”

Shankar finds the blood results very plausible, given A-beta’s evident attraction for cell membranes. The CE fraction of blood, he says, “holds a lot of promise as another compartment to look at with diagnostics.”