Study points to liver, not brain, as origin of Alzheimer's plaques

March 3 2011

Unexpected results from a Scripps Research Institute and ModGene, LLC study could completely alter scientists' ideas about Alzheimer's disease—pointing to the liver instead of the brain as the source of the "amyloid" that deposits as brain plaques associated with this devastating condition. The findings could offer a relatively simple approach for Alzheimer's prevention and treatment.

The study was published online today in *The Journal of Neuroscience Research.*

In the study, the scientists used a mouse model for Alzheimer's disease to identify genes that influence the amount of amyloid that accumulates in the brain. They found three genes that protected mice from brain amyloid accumulation and deposition. For each gene, lower expression in the liver protected the mouse brain. One of the genes encodes presenilin—a cell membrane protein believed to contribute to the development of human Alzheimer's.

"This unexpected finding holds promise for the development of new therapies to fight Alzheimer's," said Scripps Research Professor Greg Sutcliffe, who led the study. "This could greatly simplify the challenge of developing therapies and prevention."

An estimated 5.1 million Americans have Alzheimer's disease, including nearly half of people age 85 and older. By 2050, the number of people age 65 and over with this disease will range from 11 million to 16

million unless science finds a way to prevent or effectively treat it. In addition to the human misery caused by the disease, there is the unfathomable cost. A new report from the Alzheimer's Association shows that in the absence of disease-modifying treatments, the cumulative costs of care for people with Alzheimer's from 2010 to 2050 will exceed $20 trillion.

A Genetic Search-and-Find Mission

In trying to help solve the Alzheimer's puzzle, in the past few years Sutcliffe and his collaborators have focused their research on naturally occurring, inherited differences in neurological disease susceptibility among different mouse strains, creating extensive databases cataloging gene activity in different tissues, as measured by mRNA accumulation. These data offer up maps of trait expression that can be superimposed on maps of disease modifier genes.

As is the case with nearly all scientific discovery, Sutcliffe's research builds on previous findings. Several years ago, researchers at Case Western Reserve mapped three genes that modify the accumulation of pathological beta amyloid in the brains of a transgenic mouse model of Alzheimer's disease to large chromosomal regions, each containing hundreds of genes. The Case Western scientists used crosses between the B6 and D2 strains of mice, studying more than 500 progeny.

Using the results from this study, Sutcliffe turned his databases of gene expression to the mouse model of Alzheimer's, looking for differences in gene expression that correlated with differences in disease susceptibility between the B6 and D2 strains. This intensive work involved writing computer programs that identified each genetic difference that distinguished the B6 and D2 genomes, then running mathematical correlation analysis (known as regression analysis) of each difference. Correlations were made between the genotype differences

(B6 or D2) and the amount of mRNA product made from each of the more than 25,000 genes in a particular tissue in the 40 recombinant inbred mouse strains. These correlations were repeated 10 times to cover 10 tissues, the liver being one of them.

"A key aspect of this work was learning how to ask questions of massive data sets to glean information about the identities of heritable modifier genes," Sutcliffe said. "This was novel and, in a sense, groundbreaking work: we were inventing a new way to identify modifier genes, putting all of these steps together and automating the process. We realized we could learn about how a transgene's pathogenic effect was being modified without studying the transgenic mice ourselves."

Looking for a Few Good Candidates

Sutcliffe's gene hunt offered up good matches, candidates, for each of the three disease modifier genes discovered by the Case Western scientists, and one of these candidates—the mouse gene corresponding to a gene known to predispose humans carrying particular variations of it to develop early-onset Alzheimer's disease—was of special interest to his team.

"The product of that gene, called Presenilin2, is part of an enzyme complex involved in the generation of pathogenic beta amyloid," Sutcliffe explained. "Unexpectedly, heritable expression of Presenilin2 was found in the liver but not in the brain. Higher expression of Presenilin2 in the liver correlated with greater accumulation of beta amyloid in the brain and development of Alzheimer's-like pathology."

This finding suggested that significant concentrations of beta amyloid might originate in the liver, circulate in the blood, and enter the brain. If true, blocking production of beta amyloid in the liver should protect the brain.

To test this hypothesis, Sutcliffe's team set up an in vivo experiment using wild-type mice since they would most closely replicate the natural beta amyloid-producing environment. "We reasoned that if brain amyloid was being born in the liver and transported to the brain by the blood, then that should be the case in all mice," Sutcliffe said, "and one would predict in humans, too."

The mice were administered imatinib (trade name Gleevec, an FDA-approved cancer drug), a relatively new drug currently approved for treatment of chronic myelogenous leukemia and gastrointestinal tumors. The drug potently reduces the production of beta amyloid in neuroblastoma cells transfected by amyloid precursor protein (APP) and also in cell-free extracts prepared from the transfected cells. Importantly, Gleevec has poor penetration of the blood-brain barrier in both mice and humans.

"This characteristic of the drug is precisely why we chose to use it," Sutcliffe explained. "Because it doesn't penetrate the blood-brain barrier, we were able to focus on the production of amyloid outside of the brain and how that production might contribute to amyloid that accumulates in the brain, where it is associated with disease."

The mice were injected with Gleevec twice a day for seven days; then plasma and brain tissue were collected, and the amount of beta amyloid in the blood and brain was measured. The findings: the drug dramatically reduced beta amyloid not only in the blood, but also in the brain where the drug cannot penetrate. Thus, an appreciable portion of brain amyloid must originate outside of the brain, and imatinib represents a candidate for preventing and treating Alzheimer's.

As for the future of this research, Sutcliffe says he hopes to find a partner and investors to move the work into clinical trials and new drug development.

More information: "Peripheral reduction of β-amyloid is sufficient to reduce brain Aβ: implications for Alzheimer's disease," onlinelibrary.wiley.com/doi/10 … 2/jnr.22603/abstract

Provided by The Scripps Research Institute