Liver, not brain, source of Alzheimer's

by staff report via quill - Times of India *Thursday, Mar 3 2011, 5:26am*
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> A new study has suggested that the plaques associated with Alzheimer's disease start in the liver and not in the brain—completely altering scientists' ideas about the disease.

The unexpected results could now potentially simplify the nature of Alzheimer's prevention and treatment strategies.

Researchers from the Scripps Research Institute and ModGene, L.L.C., 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.

Lead author Prof Greg Sutcliffe and his collaborators used the results from a previous study by Case Western Reserve researchers to solve the Alzheimer's puzzle.

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.

These correlations were repeated 10 times to cover 10 tissues, the liver being one of them.

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," said Sutcliffe.

"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," he added.

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.

"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 and one would predict in humans, too," said Sutcliffe.

The mice were administered imatinib (trade name Gleevec), a relatively new drug currently approved for treatment of chronic myelogenous leukemia and gastrointestinal tumours.

The drug potently reduces the production of beta amyloid in neuroblastoma cells.

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 researchers found that 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.

"This unexpected finding holds promise for the development of new therapies to fight Alzheimer's," said Sutcliffe.

"This could greatly simplify the challenge of developing therapies and prevention," he added.

The study has been published online in *The Journal of Neuroscience Research*.

http://tinyurl.com/4qf9ohl
