Natural Alzheimer's weapon suggests better treatment

June 20 2011

Dr. Anil G. Cashikar (left) and Graduate Student Juhi Ojha have identified a natural mechanism for managing high levels of toxic amyloid beta peptide that occurs in Alzheimer's disease. Credit: Phil Jones/GHSU photograhper

Scientists have shown a molecular chaperone is working like a waste management company to collect and detoxify high levels of toxic amyloid beta peptide found in Alzheimer's disease.

It was known that the molecular chaperone, HspB1, was present in the hallmark plaque of Alzheimer's patients but its role remained a mystery.

"What we have found is HspB1 is a protective mechanism that tries to get rid of the toxic oligomers or aggregates of amyloid beta that occur in Alzheimer's," said Dr. Anil G. Cashikar, Biochemist at Georgia Health

Sciences University's Center for Molecular Chaperones and Radiobiology. He is corresponding author of the study published in Molecular and Cellular Biology.

Amyloid beta peptide, or Abeta, is believed to start the cascade of events that leads to brain cell damage and death in Alzheimer's: as levels increase, the peptide starts clumping in the brain. In fact, high levels in the spinal fluid are a diagnostic marker for the disease. Molecular chaperones are known for their propensity to respond to disease-producing misfolded proteins, which is how the body views excessive Abeta.

While resulting plaques occupy prime real estate in the brain, it's still better than toxic Abeta killing neurons, Cashikar said. "We think maybe the system gets overwhelmed."

Acknowledging much work remains, the scientist is excited about identifying the protective mechanism and exploring its treatment potential.

Earlier this year, a paper Cashikar published in PLoS One showed deleting genes with a similar function from a mouse model of Alzheimer's worsened disease symptoms. The new study also showed neurons from HspB1-deficient mice were more sensitive to the toxic ravages of Abeta.

"HspB1 is present because its function is to protect cells. The implication is if we can elevate the levels of this molecular chaperone, we may be able to handle the situation a little better," Cashikar said.

He wants to exploit this natural system by developing a smaller version of the molecular chaperone that could be put into the bloodstream to leach excess Abeta from the brain. The brain has a natural protective

mechanism that likely would prevent its direct application. However, the natural affinity of amyloid beta and HspB1 indicates a more distant approach could be effective. "We want to come up with smaller versions of HspB1 that can be put into the bloodstream so you can sop up the material from the brain into the blood where it can be cleared more efficiently." He also wants to explore a way to increase brain cells' natural production of protective HspB1.

Neurons actually also make the Abeta believed to attack them in Alzheimer's. The peptide's normal function in the brain is not clear, but early evidence suggests it could be involved in synaptic pruning, which is essential for memory formation. Synapses connect neurons and some existing connections must be cut for new connections and memories to be made. Why neurons start making too much Abeta and how its overproduction can be controlled are million-dollar questions, Cashikar said.

A related ongoing debate is whether the amyloid plaques and neurofibrillarly tangles, insoluble globs of protein also found in Alzheimer's, are a cause or result of the disease. Cashikar's work as well as new studies on the neurofibrillarly tangles, suggest both are protective mechanisms. Also, there is evidence of both in the brains of some healthy, elderly individuals.

GHSU Graduate Student Juhi Ojha is first author on the paper.

Provided by Georgia Health Sciences University