Mechanism of Alzheimer's suggests combination therapy needed

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Researchers at the University of Illinois at Chicago College of Medicine have discovered a mode of action for mysterious but diagnostic protein snarls found in the brains of Alzheimer's patients that suggests a one-two punch of therapy may be needed to combat the neurodegenerative disease.

Alzheimer's disease, which may affect as many as 5 million Americans and is among the most costly diseases to society in the United States and Europe, is characterized by two distinctive protein malformations: amyloid plaques and tau tangles. Amyloid plaques are sticky deposits made up of a short protein called amyloid beta, and tau tangles are made of short filaments of the tau protein.

So far no one has been able to explain how amyloid beta and the tau tangles wreak their damage on the nervous system.

"We have known for a long time that amyloid beta was bad," said Scott Brady, professor and head of anatomy and cell biology at the UIC College of Medicine. "What we haven't understood is why it's bad."

The findings, reported in a new study appearing in the Proceedings of the National Academy of Sciences Online Early Edition for March 16-20, suggest promising new targets for combination therapy.

In previous work, published earlier this year, the researchers suggested how tau tangles work together with amyloid beta to create a perfect

storm that destroys neural function and memory.

"Cell death occurs at a very late stage of the disease," said Brady, principal investigator of the study. "Long before the cells die they lose function, and that function is critical for the symptoms that we see."

Brady and his colleagues found that when short assemblies of amyloid -- rather than the long-chain plaques -- get inside neurons, they interfere with the cells' transport system. This limits their ability to send vital proteins and vesicles to where they are needed within the cell and interferes with the synaptic connections to other nerve cells.

"We know from study of several hereditary adult-onset neurodegenerative diseases that damage to the transport system, over time, results in loss of synaptic activity, a gradual dying back of the neurons, and eventual neuron death -- exactly the pattern of Alzheimer's disease progression," Brady said.

"Neurons have an enormous logistical problem," Brady said. "Their critical role in making connections may require them to be very large. Some of them have to reach half the body's length -- for a tall person, a meter or more." Even just within the brain, he said, neurons are tremendously long compared to other cells.

The fast axonal transport system responsible for moving proteins and vesicles from the neuron's cell body where they are made, down the long, trunk-like projection of the axon, to the functional areas where they are needed and back again depends on motor proteins that attach to the cargo -- a vesicle or protein -- and carry it along a track made of microtubules.

In the new study, Brady and his colleagues showed that the short assemblies of amyloid activate a transport-regulatory enzyme called CK2

that causes the motor protein to drop its cargo. They were also able to show that inhibition of CK2 is sufficient to prevent the effects of amyloid on transport.

In the earlier work, the researchers showed that tau tangles halt transport to the neuron periphery through other regulatory enzymes by causing the motor protein to release the microtubule track.

The researchers found that the CK2 activated by amyloid also works as a primer for one of the enzymes activated by tau tangles, GSK3.

"Now we have the perfect storm," said Brady. "Both amyloid and tau tangles cause problems. But when you put them together, you exacerbate the problems, creating the cascade of events that cause Alzheimer's loss of neural connections.

"It makes sense of why both have to be present to have Alzheimer's," he said.

"It is also telling us that treating one is not going to be sufficient," he said. "We're going to have to think in terms of combination therapies that will allow us to address many targets at once. This may explain why attempts to manipulate one or the other haven't been successful in patients."

Source: University of Illinois at Chicago (news : web)