Novel Role of Protein in Generating Amyloid # Peptide

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A defining hallmark of Alzheimer's disease is the accumulation of the amyloid # protein (A#), otherwise known as "senile plaques," in the brain's cortex and hippocampus, where memory consolidation occurs. Researchers at the University of California, San Diego School of Medicine have identified a novel protein which, when over-expressed, leads to a dramatic increase in the generation of A#. Their findings, which indicate a potential new target to block the accumulation of amyloid plaque in the brain, will be published in the May 1 issue of the *Journal of Biological Chemistry*.

"The role of the multi-domain protein, RANBP9, suggests a possible new therapeutic target for Alzheimer's disease," said David E. Kang, PhD, assistant professor of neurosciences at UC San Diego and director of this study.

The neurotoxic protein A# is derived when the amyloid precursor protein (APP) is "cut" by two enzymes, #-secretase (or BACE) and #-secretase (or Presenilin complex.) However, inhibiting these enzymes in order to stop the amyloid cascade has many negative side effects, as these enzymes also have various beneficial uses in brain cells. So the researchers looked for an alternative way to block the production of amyloid beta.

In order for cleavage to occur, the APP needs to travel to cholesterol-enriched sites within the cell membrane called RAFTS, where APP interacts with the two enzymes. It is this contact that the researchers sought to block.

Kang explains that the researchers identified the RANBP9 protein by studying low density lipoprotein receptor-related protein (LRP), a protein that rapidly shuttles A# out of the brain and across the blood-brain barrier to the body, where it breaks down into harmless waste products. A small segment of LRP can also stimulate A# generation, and the scientists narrowed this segment down to a 37-amino-acid stretch that can lead to changes in A#.

"RANBP9 is one of the proteins we identified that interacted with this LRP segment, but one that had never before been associated with disease-related neuronal changes," said Kang. "We discovered that this protein interacts with three components involved in A# generation - LRP, APP and BACE1 - and appears to 'scaffold' them into a structure."

Kang explained that these three components must come together to result in the first cut or cleaving that leads to production of A#. To test this, the scientists knocked out RANBP9 in the cell, and discovered that 60% less A# was produced.

"This unique factor enhances the production of beta amyloid," said Kang. "Inhibiting the RANBP9 protein may offer an alternative approach to therapy, by preventing contact between APP and the enzyme that makes the cut essential to produce amyloid plaques." The researchers' next step is to verify these findings in animal models.

According to the Alzheimer's Association, an estimated 5.3 million people have Alzheimer's disease in the United States alone, and a new case is diagnosed every seven seconds. Madepalli K. Lakshmana, Ph.D.,

the study's first author, added that "this study is the first to identify RANBP9 as a target to potentially inhibit the movement of APP to RAFTS so that amyloid beta peptide generation can be prevented. As such, a small molecule drug that can reduce the RANBP9 protein levels could offer an effective treatment for Alzheimer's disease."

Additional contributors to the study include Il-Sang Yoon, Eunice Chen and Edward H. Koo, of UC San Diego Department of Neurosciences; and Elizabetta Bianchi from the Institut Pasteur in Paris.

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