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UCSB Scientists Make Headway in Understanding Alzheimer's Disease

Scientists at UC Santa Barbara have discovered that a protein called BAG2 is important for understanding Alzheimer's disease and may open up new targets for drug discovery. They are ready to move from studying these proteins in culture to finding out how they work with mice.

In a paper published this week in the Journal of Neuroscience, the scientists describe important activities of BAG2 in cleaning up brain cells. The protein tau is normally found in brain cells, but scientists don't know why it clumps into tangles in people with Alzheimer's disease.

Senior author Kenneth S. Kosik, co-director of UCSB's Neuroscience Research Institute, and Harriman Chair in Neuroscience, has been involved in the study of neurons that develop neurofibrillary tangles, one of the hallmarks of the disease, since he was a postdoctoral fellow. "Early on in my career, we were one of several labs to discover that tau was in the neurofibrillary tangles," said Kosik.

Kosik's team recently started to work on BAG2 to find out how it may be involved in the removal of tangled tau. "It turns out that when you put this protein into the cell, it clears away the damaged tau very nicely," said Kosik. It doesn't clear away all the tau; it goes for the damaged tau protein and removes it.

For unknown reasons, when tau accumulates in a neurofibrillary tangle, the cell can't get rid of it. "All cells including neurons have an elaborate, sophisticated, elegant system for disposing of proteins," said Kosik. "Proteins have a certain turnover; sometimes they get damaged. The cell has its own trash can called the proteosome, and damaged proteins are deposited there.

"We've done this experiment many ways," said Kosik. "We've discovered a bit about how BAG2 works. We've turned it on to remove tau. We've turned it off to increase tau. We've really done a lot of manipulations using cell culture." So BAG2 is a new player, a new protein that may be a good target for study in the research of Alzheimer's disease.

"There is nothing about a drug or a treatment in any of these findings; however, the first step in fighting any illness is finding what you want to target the drug to," said Kosik. "This is a protein that is involved in neurofibrillary tangles, so now we have a new target for drug discovery. This is not a drug or a treatment, just a new target. The new target is BAG2." Kosik is looking forward to studying BAG2 in mice.

Kosik explained that we all have these proteins in our cells; however, they can go awry. Their levels can be off, or they may malfunction in another way. The same normal protein can begin to malfunction.

"It may be that BAG2 is not doing its job right; it may be that BAG2 is overwhelmed, because sometimes tau is building up, and there is not enough BAG2 there," said Kosik. "We cannot conclude from this that BAG2 is the fundamental problem in the disease state. It is only a possible target that can help us find our way out of the disease."

However, as Kosik explained, the current project started when he and his team suspected that one of the problems in Alzheimer's disease is to find out why the cell fails to dispose of tau and degrade it. They knew, even before starting the project, that the cell has marked the tau protein in Alzheimer's disease for degradation. There is a marker on the tau protein in the neurofibrillary tangles, which indicates that this is a protein that should go to the trash. The marker is called ubiquitin.

Previously, Kosik's team found a protein that is involved in the decision to throw away tau. That protein is called CHIP, and Kosik's team published information on that about four years ago.

"We knew something was going on there," said Kosik. "CHIP has a dual function. It calls out to the cell and says there is a protein here that is at a critical juncture. If the protein is salvaged, then CHIP goes off tau, and tau goes back to being a normal protein. But if the protein cannot be salvaged because it is so badly damaged, then CHIP goes into action and marks the tau for degradation by putting on several ubiquitins, and that's the signal to go to the trash."

Kosik has a very interdisciplinary lab, which he said increases the richness of this paper. The first two co-authors are Daniel C. Carretiero, postdoctoral fellow, and Israel Hernandez, graduate student. Both are molecular biologists. Co-author Pierre Neveu works in Kosik's lab, as well as UCSB's Kavli Institute for Theoretical Physics. Neveu brought in a number of computational insights that enhanced the findings.

[RETURN TO TOP]

† Top photo: These images of neurons in culture are labeled in red with an antibody to tau protein. The one on the right has a reduced level of BAG 2 and therefore tau protein has increased, as indicated by a brighter appearance.

†† Middle photo: From left, Kenneth S. Kosik, Pierre Neveu, and Israel Hernandez in the lab where they conducted their Alzheimer's disease research. Photo by George Foulsham, UCSB Public Affairs

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