Scientists Propose New Model for Alzheimer's Disease (Podcast)

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(PhysOrg.com) -- A study from the Buck Institute for Age Research offers a revolutionary new model for Alzheimer's disease (AD), a devastating neurodegenerative disorder which afflicts 24 million people worldwide. In an effort to unravel the normal function of a protein implicated in AD, scientists in California and France have discovered a naturally occurring protein that provides a new therapeutic target for the disease.

The finding upsets the current theory that AD is a disease of toxicity stemming from damage caused by sticky plaques that collect in the brain - this research points to the condition as a disorder involving an imbalance in signaling between neurons. The study appears online in the Nature publication Cell Death and Differentiation.

One of the mysteries of AD has been the normal function of the amyloid precursor protein (APP) which are concentrated at the points where neurons connect. Even though the sticky amyloid plaques which have been viewed as a hallmark sign of AD result from APP, it seems unlikely that APP exists simply to cause Alzheimer's disease. In their study, scientists from the Buck Institute and the CNRS (Centre Nationale de la Recherche Scientifique) show that APP binds to netrin-1, a protein that helps to guide nerves and their connections in the brain, as well as helping nerve cells to survive. When netrin-1 was given to mice that have a gene for Alzheimer's disease their symptoms were reversed, and the sticky amyloid was reduced.

These results suggest that the long-held belief that AD is caused by brain cell damage inflicted by the amyloid plaques may be wrong; instead, it is beginning to appear that the disease stems from an imbalance between the normal making and breaking of connections in the brain, with netrin-1 supporting the connections and the amyloid breaking the connections -- both by binding to APP and activating normal cell programs. Not only did the netrin-1 binding to APP keep the nerve cells alive and connected, but it also shut down the production of the amyloid, all of which makes it an interesting potential therapeutic.

“I think we’re going to see an explosion in the next five years involving the dissection of these signaling pathways whose imbalance leads to Alzheimer’s disease,” said Buck Institute Faculty Member Dale Bredesen, MD, who led the California half of the French-Californian collaborative research. “We now believe that APP is part of a ‘plasticity module’ that functions in normal memory and forgetting, and that netrin-1 gives us an important starting point to restore the normal balance.”

“We believe that Alzheimer’s disease is somewhat analogous to cancer, which results from an imbalance between the normal processes that support cell survival and those that cause cell turnover,” said Patrick Mehlen, PhD, Director of the Apoptosis, Cancer and Development CNRS Laboratory at the University of Lyon and co-senior author of the study. “Our hope is that this research will lead to therapeutics that will be used to address this imbalance much earlier in the disease process.”

Research is underway to develop a drug based on the findings. The Buck Institute and the CNRS in Lyon are partnering with Neurobiological Technologies Inc., to bring the discovery from the laboratory to clinical trials.

Other researchers involved in the study include first author Filipe

Calheiros Lourenço, of the University of Lyon, along with co-workers Joanna Fombonne, Véronique Corset and Fabien Llambi; Verónica Galvan of the Buck Institute, and Ulrike Müller of the University of Heidelberg. The work was supported by the Agence Nationale de la Recherche, the CNRS (Centre Nationale de la Recherche Scientifique), the National Institutes of Health, the Joseph Drown Foundation, the John Douglas French Foundation, and the Alzheimer's Association.

Provided by Buck Institute