Scientists find potential strategy to eliminate poisonous protein from Alzheimer brains

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Scientists at the Gladstone Institute of Neurological Disease (GIND) have identified a new strategy to destroy amyloid-beta (AB) proteins, which are widely believed to cause Alzheimer's disease (AD). Li Gan, PhD, and her coworkers discovered that the activity of a potent AB-degrading enzyme can be unleashed in mouse models of the disease by reducing its natural inhibitor cystatin C (CysC).

All of us produce AB proteins in the brain. However, in most people, the proteins never build up to dangerous levels because they are cleared away by enzymes that destroy them. Previously Dr. Gan's laboratory had shown that cathepsin B (CatB) is such an AB-degrading enzyme. In the latest issue of the journal *Neuron*, the researchers report a highly effective approach to promote CatB-mediated clearance of AB .

"Many groups have developed drugs to block the production of AB, but the efficacy and safety of this approach remains to be demonstrated in clinical trials," said GIND Director Lennart Mucke, MD "By identifying an effective strategy to enhance the removal of AB, this research provides a very promising alternative or complementary therapeutic avenue."

High levels of AB in the brain may result from overproduction of AB or from an inability to eliminate it from the brain. While most work has focused on the first option, the latter has been problematic. For example, efforts to develop a vaccine that would trigger the immune system to eliminate AB have shown limited success and resulted in adverse side

effects.

"Our strategy to harness the activity of a powerful AB-degrading enzyme takes advantage of the brain's own defense system to remove the toxic AB build-up," said Dr. Gan. "In principle, one could boost the activity of CatB by expressing more of it in the brain or by reducing the activity of CysC, its natural inhibitor. We focused on the latter strategy because it has greater long-term therapeutic potential."

Many enzymes that degrade proteins are kept in check by regulators called protease inhibitors. The activity of CatB is regulated by the protease inhibitor CysC. By reducing CysC activity, the scientists were able to unleash the AB-degrading power of CatB, effectively preventing the build-up of AB in mouse models of AD.

To examine the impact of this manipulation on brain function, Dr. Gan's team measured brain cell activities that relate closely to learning and memory. Increasing CatB activity by lowering CysC levels prevented AB-induced deficits in those cellular activities. The investigators also tested the modified AD mice for learning and memory in a water maze. Higher levels of CatB activity improved the ability of AD to learn the maze and to retain the new information. Increasing CatB activity also prevented the premature mortality that is typically seen in these Alzheimer models.

"Our results suggest that CysC reduction has major therapeutic potential," Dr. Gan said. "The next step will be to develop pharmacological approaches to inhibit CysC in the human brain."

Source: Gladstone Institutes