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MOLECULE REDUCES ALZHEIMER PLAQUES IN BRAIN, RESEARCHERS REPORT

The highways and byways through which the brain exchanges messages require maintenance much as any municipal road. Crucial to these thoroughfares are the trash collectors, which prevent the accumulation of toxic waste. What would happen if such debris were left to accumulate? Alzheimer's disease would result.

Unfortunately, that scenario plays itself out over and over again in the brains of the four million Americans with the disease. Now, researchers at the Gladstone Institute of Neurological Disease and the Department of Neurology at the University of California, San Francisco (UCSF) have identified a molecule that could be key to getting trash-collecting cells, called microglia, back to work.

Called TGF- β 1, the molecule stimulates microglial cells to action so they begin to clear away a toxic substance called β -amyloid, which accumulates in Alzheimer brains in the form of deposits, called plaques. Most surprising is that researchers had long viewed activated microglia primarily as the cells that incite inflammation and fuel the disease process.

"People always thought that inflammation and microglial activation were bad," said Tony Wyss-Coray, PhD, lead author, investigator at the Gladstone Institute of Neurological Disease and assistant professor of neurology at UCSF. "But we showed that, when stimulated by TGF- β 1, microglial activities can be beneficial."

Wyss-Coray and his collaborators realized they were on to something when they measured Alzheimer-like changes in mice that were genetically engineered with the capability of producing both human β -amyloid and TGF- β 1. Increased levels of TGF- β 1 reduced the number of plaques by 75% and overall β -amyloid levels by 60%, compared to mice with normal levels of TGF- β 1.

For confirmation, the investigators then took microglial cells and placed them in petri dishes along with β -amyloid. They then added TGF- β 1 to some of the dishes. Eighteen hours later, they checked to see how much β -amyloid was left and found that TGF- β 1 had triggered the microglia to destroy most of the β -amyloid in the dish, similar to what happened in the mice. The results are published in the May 2001 issue of the journal *Nature Medicine*.

(more)

Since TGF- β 1 has many effects other than those revealed in this study, physicians probably won't be using TGF- β 1 to treat patients. More promising would be to zero in on the molecules that microglia produce when they are stimulated by TGF- β 1. Such factors could be useful for treating or preventing the accumulation of β -amyloid in Alzheimer's disease, Wyss-Coray explained.

Co-investigators on the study include Lennart Mucke, MD, director of the Gladstone Institute of Neurological Disease and Joseph B. Martin Distinguished Professor of Neuroscience at UCSF; Gladstone research associates Carol Lin, Fengrong Yan, Gui-Qiu Yu, and Michelle Rohde; Lisa McConlogue, PhD, staff scientist at Elan Pharmaceuticals; and, Eliezer Masliah, MD, professor of pathology and neurosciences at the University of California, San Diego.

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The Gladstone Institute of Neurological Disease is one of three research institutes that comprise The J. David Gladstone Institutes, a private biomedical research institution affiliated with UCSF. The institution is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing personal interest in medical education and research.

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