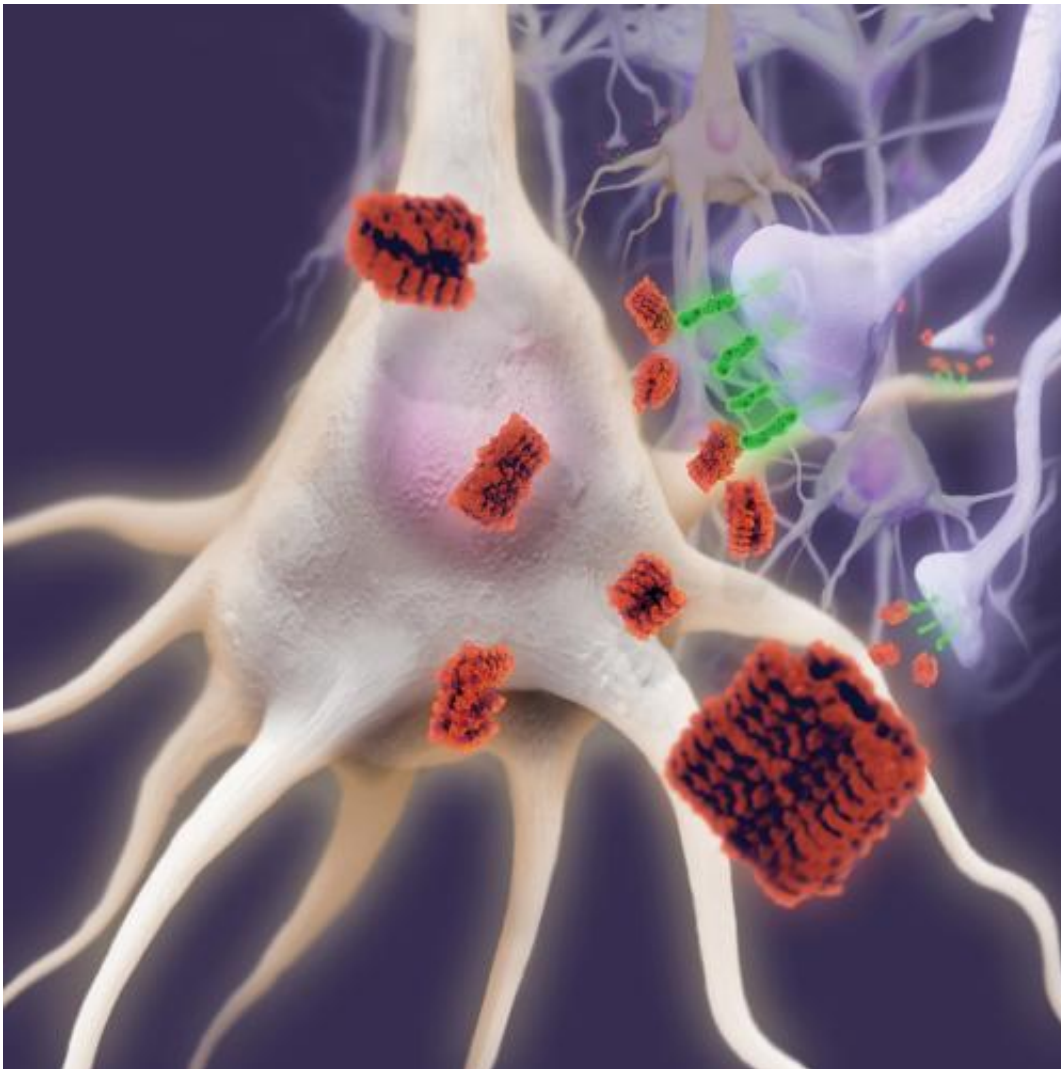


Scientists reveal how beta-amyloid may cause Alzheimer's

September 19 2013



Artist rendering of β -amyloid oligomers (red) and receptor LILRB2 or PirB (green) in neuronal synapses of Alzheimer's brains. Inhibitory immune receptors LILRB2 in human brain and its murine ortholog PirB were discovered to act as neuronal receptors for β -amyloid oligomers, which contribute to synaptic

dysfunction and memory defects in Alzheimer's disease. Credit: Eric Smith, Carla Shatz, and Taeho Kim

Scientists at the Stanford University School of Medicine have shown how a protein fragment known as beta-amyloid, strongly implicated in Alzheimer's disease, begins destroying synapses before it clumps into plaques that lead to nerve cell death.

Key features of Alzheimer's, which affects about 5 million Americans, are wholesale loss of [synapses](#)—contact points via which [nerve cells](#) relay signals to one another—and a parallel deterioration in [brain function](#), notably in the ability to remember.

"Our discovery suggests that Alzheimer's disease starts to manifest long before [plaque formation](#) becomes evident," said Carla Shatz, PhD, professor of neurobiology and of biology and senior author of a study that will be published Sept. 20 in *Science*.

Investigators at Harvard University also contributed to the study. The research, conducted in mice and in human brain tissue, may help to explain the failures in recent years of large-scale clinical trials attempting to slow the progression of Alzheimer's by pharmacologically ridding the brain of amyloid plaques. It may also point the way to better treatments at earlier stages of the disease.

Beta-amyloid begins life as a solitary molecule but tends to bunch up—initially into small clusters that are still soluble and can travel freely in the brain, and finally into the plaques that are hallmarks of Alzheimer's. The study showed for the first time that in this clustered form, beta-amyloid can bind strongly to a receptor on nerve cells, setting in motion an intercellular process that erodes their synapses with other

nerve cells.

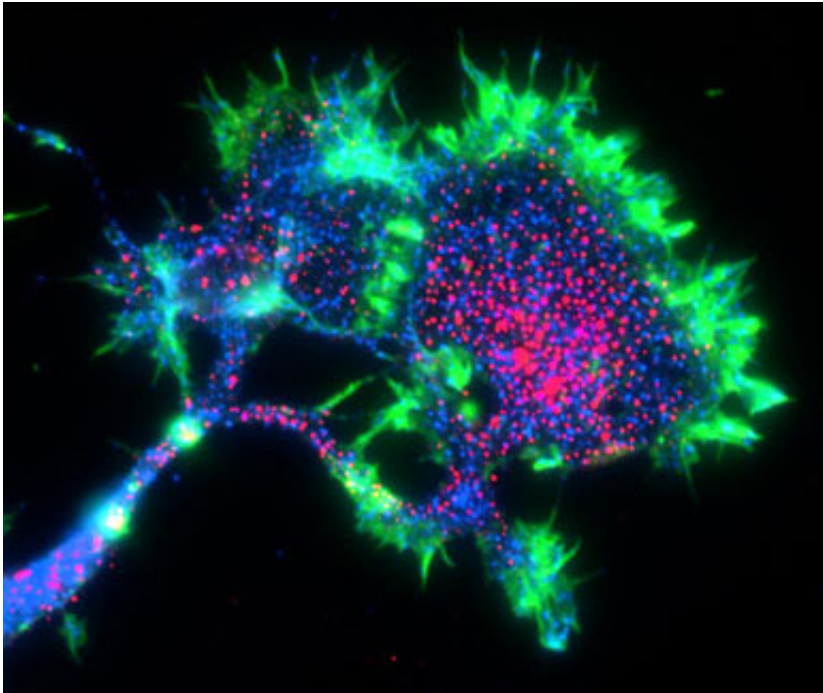
Synapses are the connections between nerve cells. They are essential to storing memories, processing thoughts and emotions, and planning and ordering how we move our bodies. The relative strength of these connections, moreover, can change in response to [new experiences](#).

Using an experimental mouse strain that is highly susceptible to the synaptic and cognitive impairments of Alzheimer's disease, Shatz and her colleagues showed that if these mice lacked a surface protein ordinarily situated very close to synapses, they were resistant to the memory breakdown and synapse loss associated with the disorder. The study demonstrated for the first time that this protein, called PirB, is a high-affinity receptor for beta-amyloid in its "soluble cluster" form, meaning that soluble beta-amyloid clusters stick to PirB quite powerfully. That trips off a cascade of biochemical activities culminating in the destruction of synapses.

Shatz is the Sapp Family Provostial Professor, as well as the director of Bio-X, a large Stanford interdisciplinary consortium drawing on medical, engineering and biology faculty. She has been studying PirB for many years, but in a different context. In earlier work, Shatz explored the role of PirB in the brain using genetically engineered mice that lacked it. She discovered that PirB, previously thought to be used only by cells in the immune system, is also found on nerve cells in the brain, where it slows the ability of synapses to strengthen in proportion to the extent to which they are engaged, and actually promotes their weakening. Such brakes are desirable in the brain because too-easy synaptic strength-shifting could trigger untoward consequences like epilepsy.

In the new study, Shatz's team employed a different genetically engineered mouse strain whose genome contained mutant copies of two separate human genes. Each of these mutations is known to predispose

individuals to Alzheimer's disease. When both mutations are present in mice, which ordinarily never develop [amyloid plaques](#), the result is abundant amyloid plaque deposition with advancing age, as well as an eventual decline in performance on various tests of memory.



PirB (red) is heavily concentrated on the surface of growing nerve cells. Credit: Dr. Carla Shatz, Stanford University.

"I've always found it strange that these mice—and, in fact, all the mouse models for Alzheimer's disease that we and other people study—seem not to have any problems with memory until they get old," Shatz said. "These mice's brains have high levels of beta-amyloid at a very early age."

Shatz found herself wondering if there might be a more sensitive measure of beta-amyloid's early effects on young brains. A study she co-

authored in 2012 demonstrated that a particular mouse brain region, whose constituent synapses are normally quite nimble at shifting their relative strengths in response to early-life experiences, showed no such flexibility in young Alzheimer's-prone mice. This suggested that subtle Alzheimer's-related effects might appear far earlier than plaques or memory loss do.

Now, Shatz wondered whether eliminating PirB from the Alzheimer's mouse strain could restore that flexibility. So her team bred the Alzheimer's-genes-carrying strain with the PirB-lacking strain to create hybrids. Experimentation showed that the brains of young "Alzheimer's mice" in which PirB was absent retained as much synaptic-strength-shifting flexibility as those of normal mice. PirB-lacking Alzheimer's mice also performed as well in adulthood as normal mice did on well-established tests of memory, while their otherwise identical PirB-expressing peers suffered substantial synapse and memory loss.

"The PirB-lacking Alzheimer's mice were protected from the beta-amyloid-generating consequences of their mutations," Shatz said. The question now was, why?

Taeho Kim, PhD, a postdoctoral scholar in Shatz's lab and the lead author of the new study, advanced a hypothesis he had cooked up in 2011 while describing his research to a captive audience of one—his then-4-year-old son, whom he was driving to the Monterey Bay Aquarium: Maybe PirB and beta-amyloid were binding. This might cause PirB to stomp on the brakes even more than it usually does, weakening synapses so much they could disappear altogether, taking memories with them.

Further experiments showed that, indeed, beta-amyloid binds strongly to PirB. While PirB is specifically a mouse protein, Kim also identified for the first time an analogous beta-amyloid receptor in the human brain: a

protein called LirB2.

In another experiment, Kim compared proteins in the brains of PirB-lacking Alzheimer's mice to those in the brains of PirB-expressing Alzheimer's mice. The latter showed significantly increased activity on the part of a few workhorse proteins, notably an enzyme called cofilin. Subsequent studies also found that cofilin activity in the brains of autopsied Alzheimer's patients is substantially higher than in the brains of people without the disorder.

Here the plot thickens: Cofilin works by breaking down actin, a building-block protein essential to maintaining synaptic structure. And, as the new study also showed, beta-amyloid's binding to PirB results in biochemical changes to cofilin that revs up its actin-busting, synapse-disassembling activity.

"No actin, no synapse," Shatz said.

Kim's hypothesis appears to have been correct. Beta-amyloid binds to PirB (and, the researchers proved, to its human analog, LirB2), boosting cofilin activity and busting synapses' structural integrity.

Although there may be other avenues of destruction along which synapses are forced to walk, Shatz doubts there are very many. She said she thinks the direct participation of beta-amyloid—as well as cofilin, so clearly implicated in synaptic breakdown—suggests that this pathway is important. "We looked at human brains in this study, too, and we found that a similar derangement of cofilin activity is present in Alzheimer's brains but not healthy brains," she said.

Shatz suggested that drugs that block beta-amyloid's binding to PirB on nerve-cell surfaces—for example, soluble PirB fragments containing portions of the molecule that could act as decoy—might be able to exert

a therapeutic effect. "I hope this finding will be enticing enough to pharmaceutical and biotechnology companies that someone will try pushing this idea forward," she said.

More information: Human LirB2 Is a beta-Amyloid Receptor and Its Murine Homolog PirB Regulates Synaptic Plasticity in an Alzheimer's Model," by T. Kim et al. *Science*, 2013. DOI: 10.1126/science.1242077

Provided by Stanford University Medical Center

Citation: Scientists reveal how beta-amyloid may cause Alzheimer's (2013, September 19) retrieved 27 April 2024 from

<https://medicalxpress.com/news/2013-09-scientists-reveal-beta-amyloid-alzheimer.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.