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New PrPetrator in AD

By Lev Osherovich, Senior Writer

Yale University researchers have uncovered a surprising link between Alzheimer's disease and the prion protein that has been linked to mad cow disease and the related human condition, Creutzfeldt-Jakob disease.

The team has reported that prion protein (PRNP; PrP), which itself forms aggregates in prion diseases like Creutzfeldt-Jakob disease (CJD), is one of the main cellular receptors for oligomeric β-amyloid (Aβ), the toxic misfolded protein behind AD.[1] Targeting the interaction between Aβ and PrP could thus be a new tack against AD.

Aβ is a fragment of the amyloid-β (A4) precursor protein (APP), a neuronal surface protein, and forms the hallmark amyloid aggregates that clog the brains of AD patients. However, and despite numerous theories about how the oligomers trigger neuron death, the direct molecular target of Aβ had, until now, been a mystery.

The Yale study in *Nature* now offers strong *in vitro* evidence for PrP as a specific cellular Aβ oligomer receptor.

"The mechanism by which the production of Aβ makes neurons sick has been a black box," said Stephen Strittmatter, professor of neurology at **Yale School of Medicine** and lead author on the paper. "In this study we set out to understand how a certain form of Aβ associated with disease, the oligomeric form, can interact with neurons and trigger the toxic cascade of the disease process. We identified PrP as the surface protein needed for Aβ to disrupt functions of neurons in a dish."

The findings suggest that the two proteins activate a neurodegenerative disease signaling pathway common to both AD and CJD. The results further indicate that mAbs targeting PrP could be useful in treating AD. That could be good news for **Prionics AG**, a veterinary diagnostics company that has developed a range of PrP antibodies.

Brain binding

Strittmatter's team initially suspected that recombinant Aβ oligomers interacted with cultured neurons by binding to a specific cell-surface receptor. They set out to clone this receptor by screening a cDNA expression library in cultured monkey kidney cells.

The team found that Aβ oligomers bound to the surface of cells expressing transgenic PrP but not to mock-transfected controls. The team went on to pin down the specific portion of PrP that binds to Aβ by repeating the experiment with a combination of truncated PrP mutants and antibodies that blocked various parts of PrP.

To further prove that the interaction between Aβ and PrP was relevant to brain cells, the researchers exposed cultured neurons from wild-type and PrP knockout mice to Aβ oligomers. They found that PrP-deficient neurons had much lower binding of Aβ oligomers than did wild-type neurons. This proved that PrP was at least partly responsible for Aβ oligomers binding to brain cells.

Strittmatter said his team was "absolutely surprised" that the mystery receptor turned out to be PrP, which has no known function aside from its involvement in prion diseases.

"Strittmatter goes a long way to showing that PrP is a receptor for Aβ," said Adriano Aguzzi, professor of neuropathology at **University Hospital Zurich**.

Aguzzi said he was intrigued by the connection between AD and prion diseases suggested by the study. Both disorders involve conversion of proteins from a soluble form to a misfolded, aggregated form that leads to neurotoxicity.

"It's ironic that the receptor for a misfolded protein is itself prone to aggregation," said Aguzzi.

Indeed, Strittmatter suspects that some of the downstream consequences of PrP binding may be shared between AD and CJD. "PrP could be a receptor or a nexus for aggregated and toxic proteins," he said.

Lennart Mucke, senior investigator and director of the **Gladstone Institute of Neurological Disease**, thinks PrP could be the bridge between Aβ oligomers and a number of downstream signaling molecules implicated in AD.

Mucke said PrP associates with the receptor tyrosine kinase FYN oncogene related to SRC FGR YES (FYN) and microtubule-associated protein-τ (MAPT; Tau), two proteins that modulate Aβ oligomer toxicity. PrP is also found in plasma membrane lipid rafts, which are thought to be critical action sites for Aβ oligomers.

PrP can now "assume the center position that engages other players implicated in AD pathogenesis," said Mucke. However, he noted that because the oligomers could still bind to PrP-deficient neurons, albeit with lower affinity than that for wild-type cells, there are likely to be other receptors for Aβ oligomers besides PrP.

Mucke said questions about the mechanism of PrP-facilitated Aβ toxicity, which could involve changes in cell signaling or endocytosis of oligomers captured by the receptor, could be readily answered in cell culture models developed primarily to study prion diseases.

Memory test

Indeed, the biggest question now is whether the Aβ-PrP connection has any functional significance in AD *in vivo*.

A critical test of the significance of the Aβ-PrP connection will be whether deletion of PrP delays the progression of disease in mouse models of AD. Aguzzi suspects that in light of the *Nature* study, numerous laboratories will be racing to cross PrP knockout mice into various AD models to test this hypothesis.

Strittmatter's team did have some encouraging data suggesting that the Aβ-PrP interaction can affect learning and memory, which deteriorate in AD. In cultured hippocampal slices, deletion of PrP or blockade of the receptor with antibodies protected neurons from the harmful effects of Aβ oligomers on long-term potentiation, a model of memory.

Sina Ghaemmaghami, assistant adjunct professor of neurology at the Institute for Neurodegenerative Diseases at the **University of California, San Francisco**, said that PrP had not previously been thought to play a role in memory.

"The effect they're seeing on long-term potentiation is certainly surprising, since PrP has not been linked to this before," said Ghaemmaghami. "It catches the PrP field off guard."

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>
> ***—Adriano Aguzzi, University Hospital Zurich***

Therapeutic angle

The study opens up at least two new angles of attack on AD: directly targeting PrP to prevent Aβ binding or blocking the downstream consequences of PrP engagement by Aβ.

Strittmatter thinks that targeting PrP and its downstream effectors could be combined with compounds directed against Aβ that are currently in the clinic. Most AD therapies in clinical trials involve either lowering the production of Aβ or sponging up the errant protein using mAbs.[2]

"PrP is a target in its own right but could be targeted together with Aβ-lowering agents. Also, because PrP knockout mice have very mild phenotypes, it portends for it being a relatively good target," he said.

Strittmatter thinks it should now be possible to identify the changes in cell signaling pathways triggered by Aβ binding, which could point to druggable downstream cellular targets. Recent reports have identified downstream changes in lipid metabolism and cellular signaling caused by Aβ oligomers and have suggested points of intervention for AD,[3,4] though the role of PrP in these pathways is still murky.

Prion property

The *Nature* study is potentially a boon for Prionics, a Swiss biotech that began life by developing antibody diagnostics for human and animal forms of CJD and has since branched out into other veterinary diagnostics.

Alex Räber, head of R&D, said the company has spun out most of its human therapeutics program into a new company, **Neurotune AG**, but retained one PrP-related product, an ELISA-based diagnostic for CJD.

"This *Nature* paper really shows a nice link between the prion molecule and the mechanism of AD," Räber said. Thus, the prospect of targeting the interaction between PrP and Aβ is really attractive, he added.

Räber noted that a large number of antibodies against PrP, as well as PrP-mutated mouse strains, have been developed for research purposes. Thus, he thinks it should be fairly straightforward to test whether using antibodies to block PrP's interaction with Aβ could help treat AD in mice.

According to Räber, some of Prionics' antibodies might fit this bill, although the company's IP in this space relates to prion diseases, not AD.

"We still have a patented portfolio of PrP antibodies and claims for therapeutic purposes, so we might be engaged in providing licenses for antibodies," said Räber. "If there's really a commercial possibility for using an anti-PrP antibody for AD therapy, it's still an open area."

Alternatively, Gladstone's Mucke suggested trying to disrupt Aβ-PrP binding using small molecules, because mAbs don't readily cross the blood-brain barrier. Because Strittmatter's team has mapped the specific interaction site between the two proteins, screening for small molecules to block their interaction should be fairly straightforward, said Mucke.

Strittmatter's findings are the subject of pending patents and are available for licensing from Yale University.

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COMPANIES AND INSTITUTIONS MENTIONED

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