Targeting inflammation in AD

By Lev Osherovich, Senior Writer

German researchers have implicated the inflammasome, an intracellular sensor of proinflammatory signaling, as a key player in Alzheimer's disease.¹ The findings provide additional evidence that Alzheimer's disease could be treated with anti-inflammatory agents that act upstream of β -amyloid deposition.

The accumulation of β -amyloid (A β) is thought to underlie the neurodegeneration at the heart of AD, and as a result most efforts to treat the disease have focused on directly blocking A β production or the accumulation of A β plaques.

Although the central role of A β in AD is widely accepted, Michael Heneka, professor of clinical neuroscience at the **University of Bonn**, said academic researchers observed in the 1980s "that people in advanced age either have plaques or plaques plus inflammation."

However, it was unclear whether brain inflammation is a cause or consequence of AD. "Inflammation has really been the stepchild of the AD field. People would laugh and say that inflammation is a complete bystander that is secondary to disease," Heneka said.

Now, Heneka's team has found that AD progression in mice requires the Nlr family pyrin domain containing 3 (Nlrp3; Nalp3) inflammasome. The team showed that Nalp3 inflammasome activity was essential for the accumulation of dysfunctional microglia, the brain's innate immune cells, at AD lesions.

If NALP3-mediated inflammation is indeed a key player in AD-associated inflammation, "we now know what is the motor of disease and how to stop it," said Heneka.

Prince Casp1

Heneka's team hypothesized that A β aggregates trigger proinflammatory signaling. Thus, the group tested whether known players in inflammation were active in the brains of patients with AD. Indeed, postmortem brain tissue from patients with AD and AD model mice had higher levels of IL-1 β -converting enzyme (CASP1), a protease that activates proinflammatory cytokines, than tissue from healthy controls.

The team then tested whether the NALP3 inflammasome, which activates CASP1, also played a role in AD. Indeed, AD model mice lacking either *Nalp3* or *Casp1* performed similarly to non-AD controls

in a range of neurophysiological and behavioral assays for AD-associated neurological dysfunction.

Nalp3 and *Casp1* knockouts also had lower levels of A β , suggesting that proinflammatory signaling affected either production or accumulation of amyloid plaques.

Heneka suspected this reduction of A β might relate to changes in the behavior of microglia. Indeed, microglia from *Nalp3* or *Casp1* knockout AD model mice were more effective at ingesting and disposing of A β aggregates than microglia from wild-type AD mice. Microglia from *Nalp3*-deficient AD mice had biomarkers that indicated a productive, short-lived inflammatory response, whereas microglia from wild-type AD mice had markers associated with chronic inflammation.

Altogether, Heneka's findings suggest that chronic activation of the NALP3 inflammasome in AD leads to abnormally aggressive microglia that are unable to ingest and break up A β aggregates and instead secrete neuron-killing proinflammatory cytokines and proteases.

Results were reported in *Nature*.

Nalp help

The findings argue that blocking some combination of NALP3 and its downstream effectors could be useful for treating AD. More work is needed to identify which target in this pathway would be most suitable for early intervention in AD.

Heneka is skeptical about whether blocking any steps in this pathway would be useful in patients with advanced disease and instead thinks that anti-inflammatory therapy could be useful in slowing progression of early forms of AD such as mild cognitive impairment (MCI).

"I have a hard time imagining that any of these targets would be suitable for acute treatment, but if we initiate anti-inflammatory treatment at early stages of disease, this could

prevent or delay disease," he said.

Heneka is collaborating with some of his coauthors to screen for brain-penetrating NALP3 inhibitors. He cautioned that mouse studies suggest the lack of *Nalp3* could compromise innate immunity and increase susceptibility to bacterial pathogens, so hitting this pathway might elicit side effects.

It also remains unclear whether the NALP3 pathway relates to other recently discovered inflammatory players in AD. Last November, separate teams at **deCode genetics ehf** and **University College London** identified genetic variants in the proinflammatory cell-surface receptor triggering receptor expressed on myeloid cells 2 (TREM2) that led to increased AD risk compared with that for noncarrier controls.^{2,3}

deCode is being acquired by **Amgen Inc.**

Also in November, Swiss and German researchers reported that blocking IL-12 or IL-23 signaling could reduce pathological microglial activity in AD.⁴

Heneka said that experiments are under way to clarify how the NALP3 inflammasome affects IL-12, IL-23 and TREM2 activity.

Although no companies are directly targeting NALP3 or CASP1 in

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University of Bonn**

AD, at least one biotech—**Transition Therapeutics Inc.**—has preclinical AD compounds that block proinflammatory mechanisms downstream of the inflammasome.

The results published in *Nature* are not patented.

Osherovich, L. *SciBX* 6(1); doi:10.1038/scibx.2013.3

Published online Jan. 10, 2013

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