

Inflammatory processes drive progression of Alzheimer's and other brain diseases

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Inflammation drives the progression of neurodegenerative brain diseases and plays a major role in the accumulation of tau proteins within neurons. An international research team led by the German Center for Neurodegenerative Diseases (DZNE) and the University of Bonn comes to this conclusion in the journal *Nature*. The findings are based on the analyses of human brain tissue and further lab studies. In the particular case of Alzheimer's the results reveal a hitherto unknown connection

between Abeta and tau pathology. Furthermore, the results indicate that inflammatory processes represent a potential target for future therapies.

Tau proteins usually stabilize a neuron's skeleton. However, in Alzheimer's disease, frontotemporal dementia (FTD), and other "tauopathies," these proteins are chemically altered, they detach from the cytoskeleton and stick together. As a consequence, the cell's mechanical stability is compromised to such an extent that it dies off. In essence, "[tau pathology](#)" gives neurons the deathblow. The current study led by Prof. Michael Heneka, director of the Department of Neurodegenerative Diseases and Gerontopsychiatry at the University of Bonn and a senior researcher at the DZNE, provides new insights into why tau proteins are transformed. As it turns out, [inflammatory processes](#) triggered by the brain's immune system are a driving force.

A Molecular Switch

A particular protein complex, the "NLRP3 [inflammasome](#)," plays a central role for these processes, the researchers report in *Nature*. Heneka and colleagues studied this macromolecule, which is located inside the brain's immune cells, in previous studies. It is a molecular switch that can trigger the release of inflammatory substances. For the current study, the researchers examined tissue samples from the brains of deceased FTD patients, cultured brain cells, and mice that exhibited hallmarks of Alzheimer's and FTD.

"Our results indicate that the inflammasome and the inflammatory reactions it triggers, play an important role in the emergence of tau pathology," Heneka said. In particular, the researchers discovered that the inflammasome influences enzymes that induce a hyperphosphorylation of tau proteins. This chemical change ultimately causes them to separate from the scaffold of neurons and clump together. "It appears that inflammatory processes mediated by the

inflammasome are of central importance for most, if not all, [neurodegenerative diseases](#) with tau pathology."

A Link between Abeta and Tau

This especially applies to Alzheimer's disease. Here another molecule comes into play: amyloid beta (Abeta). In Alzheimer's, this [protein](#) also accumulates in the brain. In contrast to tau proteins, this does not happen within the neurons but between them. In addition, deposition of Abeta starts in early phases of the [disease](#), while aggregation of tau proteins occurs later.

In previous studies, Heneka and colleagues were able to show that the inflammasome can promote the aggregation of Abeta. Here is where the connection to the recent findings comes in. "Our results support the amyloid cascade hypothesis for the development of Alzheimer's. According to this hypothesis, deposits of Abeta ultimately lead to the development of tau pathology and thus to cell death," said Heneka. "Our current study shows that the inflammasome is the decisive and hitherto missing link in this chain of events, because it bridges the development from Abeta pathology to tau pathology. It passes the baton, so to speak." Thus, deposits of Abeta activate the inflammasome. As a result, formation of further deposits of Abeta is promoted. On the other hand, chemical changes occur to the tau proteins resulting into their aggregation.

A Possible Starting Point for Therapies

"Inflammatory processes promote the development of Abeta pathology, and as we have now been able to show, of tau pathology as well. Thus, the inflammasome plays a key role in Alzheimer's and other brain diseases," said Heneka, who is involved in the Bonn-based

"ImmunoSensation" cluster of excellence and who also teaches at the University of Massachusetts Medical School. With these findings, the neuroscientist sees opportunities for new treatment methods. "The idea of influencing tau pathology is obvious. Future drugs could tackle exactly this aspect by modulating the immune response. With the development of tau pathology, mental abilities decline more and more. Therefore, if tau [pathology](#) could be contained, this would be an important step towards a better therapy."

More information: NLRP3 inflammasome activation drives tau pathology, *Nature* (2019). [DOI: 10.1038/s41586-019-1769-z](https://doi.org/10.1038/s41586-019-1769-z) , [nature.com/articles/s41586-019-1769-z](https://www.nature.com/articles/s41586-019-1769-z)

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