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NEURODEGENERATION

# An independent route to toxicity

> mice expressing P301S tau and APOE4 … showed markedly more brain atrophy … than other P301S/APOE mice

Of the multiple alleles that encode apolipoprotein E (APOE), the *ε4* allele (*APOE4*) is notable because it confers an increase in the risk of developing late-onset Alzheimer disease (AD). It is thought that APOE4 promotes the amyloid-β peptide-associated pathology that is found in AD, but it is unclear whether APOE4 also has an effect on tau-associated pathology, which is also a feature of this disorder. Now, Shi *et al.* show in a mouse model of tau-mediated neurodegenerative disease that APOE4 promotes the neurotoxic effects of tau.

To probe whether any relationship exists between APOE4 and tau, the authors used transgenic mice expressing a mutant variant of tau that is implicated in a form of frontotemporal dementia (P301S tau transgenic mice) crossed with human *APOE* knock-in mice or *Apoe* knockout mice; the knock-in mice expressed the *APOE4* allele or one of the two other *APOE* alleles — *APOE2* or *APOE3*.

Nine-month-old P301S tau mice expressing any one of the APOE isoforms showed greater brain atrophy than wild-type mice, *Apoe* knockout mice expressing P301S tau or mice expressing one of the APOE isoforms but no P301S tau. Moreover, mice expressing P301S tau and APOE4 (P301S/APOE4 mice) showed markedly more brain atrophy — including in the hippocampus and the piriform–entorhinal cortex — than other P301S/APOE mice. Thus, the absence of APOE seems to largely protect against the atrophy observed in the P301S/APOE mice, whereas the presence of APOE4 in such mice seems to exacerbate this atrophy.

At 3 and 9 months of age, P301S/APOE4 mice had higher levels of tau than other P301S/APOE mice or *Apoe* knockout mice expressing P301S tau. The authors found that autophagy-linked genes were downregulated in 9-month-old APOE4-expressing mice, indicating that APOE4 might reduce the autophagy-mediated clearance of tau.

Disease-associated tau may cause neurodegeneration through a direct mechanism, but it is possible that, in combination with dying neurons, it may also trigger inflammation, which in itself may be neurotoxic. Previous studies have linked APOE4 to an enhanced innate immune system response. Confirming this link, the authors showed that cultured microglia from P301S/APOE4 mice produced markedly higher levels of pro-inflammatory cytokines following lipopolysaccharide treatment than microglia from other P301S/APOE mice. Moreover, microglia from 9-month-old P301S/APOE4 mice showed upregulation of various pro-inflammatory genes.

To examine the relationship between APOE4 and neurodegeneration, they co-cultured neurons from P301S tau-expressing mice with mixed glial populations from *APOE* knock-in mice or *Apoe* knockout mice. In line with the findings in mice, the least amount of neuronal death was observed in the co-cultures that included glia from the knockout mice, whereas marked levels of neurodegeneration were observed in the presence of glia from *APOE4* knock-in mice. This neurodegeneration was associated with a high level of tumour necrosis factor, a pro-inflammatory cytokine released by microglia, suggesting that glial activation may have, at least partly, contributed to the cell death observed. Treatment of P301S tau-expressing neuron-only cultures with recombinant APOE also led to neuronal death, with APOE4 proving the most toxic APOE isoform, although the cell death was not as extensive as that seen in the co-cultures, indicating that the neuroinflammatory mechanism could occur in addition to a more direct APOE-mediated neurotoxic mechanism.

Finally, the authors examined post-mortem tissue from individuals with a primary tauopathy and found that those with the *APOE4* allele showed more regional neurodegeneration. This allele was also associated with greater disease progression in a cohort of individuals with symptomatic AD. They conclude that *APOE4* is associated with more extensive neurodegeneration in both the presence and absence of amyloid-β pathology.

Together, these data provide evidence that APOE4 may promote neurodegeneration via mechanisms that are related to tau and neuroinflammation and that are independent of any effects it may exert on amyloid-β.

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**ORIGINAL ARTICLE** Shi, Y. *et al.* ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. *Nature* **549**, 523–527 (2017)