NEURODEGENERATIVE DISEASE

Death receptor takes centre stage

DOI:
10.1038/nrn2242

Despite the existence of multiple hypotheses and years of intensive research, a full understanding of the pathogenesis of Alzheimer's disease (AD) continues to elude researchers. A new study by Shen and colleagues suggests that tumour necrosis factor type 1 death receptor (TNFR1) might be a central mediator of AD pathology.

The idea that abnormal processing of amyloid precursor protein (APP) underlies AD pathology is supported by the phenotypes of transgenic mice with aberrant APP processing. Evidence also links inflammation with pathology in both AD patients and mouse models, but how these two potentially causal pathways might be linked is unclear. The authors had previously shown that TNFR1, the receptor for the pro-inflammatory cytokine TNF-α, is crucial for amyloid-β-mediated cell death *in vitro*, and it is known that amyloid-β can bind to this receptor. Here, they investigated the interaction between these two pathways *in vivo* by crossing APP23 mice, which overexpress a mutated form of *APP*, with mice that lack the TNFR1 gene (*Tnfrsf1a*$^{-/-}$ mice).

APP23 mice exhibit extensive amyloid-β-related pathology, but this was dramatically reduced in APP23/*Tnfrsf1a*$^{-/-}$ mice. The brains of these mice contained fewer amyloid plaques, had reduced cerebral amyloid angiopathy and less evident microglial activation. Furthermore, the progressive decrease in neuron numbers that is seen in APP23 mice was almost eliminated in the APP23/*Tnfrsf1a*$^{-/-}$ mice. The authors examined the performance of the APP23/*Tnfrsf1a*$^{-/-}$ mice using a hole-board memory test, which assesses spatial learning and memory, and an object recognition task. In both cases, the removal of TNFR1 restored performance to approximately that of wild-type mice.

How does TNFR1 elimination alleviate amyloid-β-mediated pathology? The authors showed that, although APP levels were not affected by the loss of TNFR1, levels of amyloid-β were reduced. They went on to show that deletion of *Tnfrsf1a* reduces the expression of the gene that encodes an enzyme that is vital to the generation of amyloid-β, β-secretase 1 (BACE1).

Next, the authors examined the mechanisms by which TNFR1 signalling influences *Bace1* expression. In cells in which a reporter gene was driven by the *Bace1* promoter, extracellular application of TNFα increased *Bace1* promoter activity — an effect that relied on TNFR1. Further dissection of the signalling pathway revealed that the transcription factor NF-κB has an important role in the stimulation of the *Bace1* promoter by TNFR1 signalling.

These findings indicate that TNFR1 signalling, which can be activated by both inflammation and amyloid-β, may contribute to AD pathology by driving the expression of *Bace1*. The reduced neuron loss and restored memory performance that was observed when TNFR1 signalling was eliminated in a mouse model of AD suggests that this receptor might be a viable target for future therapeutic interventions.

Katherine Whalley

ORIGINAL RESEARCH PAPER He, P. *et al.* Deletion of tumor necrosis factor death receptor inhibits amyloid β generation and prevents learning and memory deficits in Alzheimer's mice. *J. Cell Biol.* **178**, 829–841 (2007)