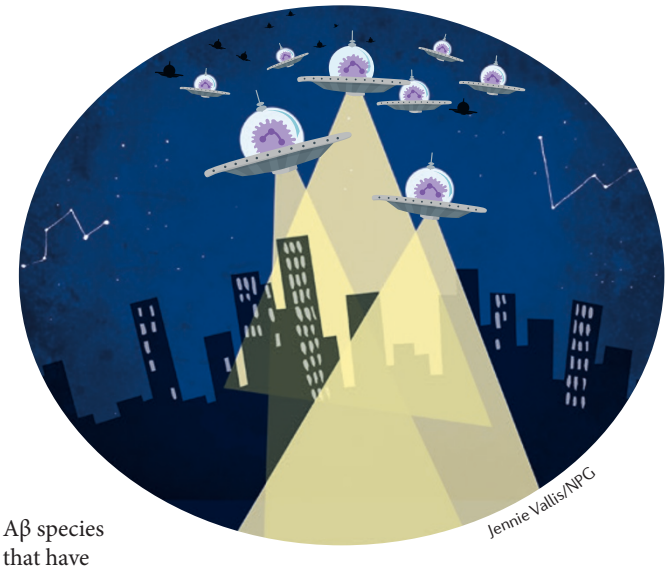
NEURODEGENERATIVE DISEASE

A neutrophil invasion



It is widely recognized that the brain's resident population of immune cells, microglia, are involved in the pathogenesis of Alzheimer disease (AD). However, the contribution of populations of blood-borne immune cells that are usually excluded from the CNS to this disease is less well understood. Zenaro *et al.* now report that the infiltration of blood-derived neutrophils into the CNS contributes to cognitive decline in animal models of AD.

Previous studies have suggested that blood–brain barrier dysfunction and the entry of blood-derived leukocytes, including neutrophils, into the brain may occur in AD. Here, the authors showed that the number of neutrophils in the brain was higher in two established mouse models of AD — the 5XFAD mouse (which overexpresses mutated forms of human amyloid precursor protein (APP) and presenilin 1 (PS1)) and the 3XTg AD mouse (which expresses mutated forms of PS1, APP and tau) — than in wild-type mice.

Using two-photon laser scanning microscopy in the cortex of 5XFAD mice, the authors showed that exogenously labelled neutrophils adhered to the endothelial lining of the brain's blood vessels before migrating into and through the parenchyma, where they often accumulated in areas of amyloid-β (Aβ) deposition. Neutrophil infiltration of the brain began before the onset of cognitive decline and peaked around the time that memory loss is first observed, suggesting that neutrophils might contribute to cognitive impairment. Indeed, depletion of neutrophils from the blood of 3XTg AD mice restored cognitive function in two behavioural tests of learning and memory.

The adhesion of neutrophils to endothelial cells is promoted by the interaction between the integrin LFA-1 (lymphocyte function-associated antigen 1), which is expressed by neutrophils, and ICAM1 (intercellular adhesion molecule 1), which is expressed by endothelial cells. The authors showed that neutrophils from mice lacking LFA-1 could not adhere to endothelial cells or migrate into the brains of 5XFAD mice. 3XTg AD mice that also lacked LFA-1 (or in which LFA-1 was inhibited with an antibody) exhibited reduced cognitive dysfunction, supporting the importance of this adhesion protein for neutrophil infiltration and subsequent AD-like pathogenesis.

What drives the invasion of neutrophils in AD? The authors observed an increase in the levels of vascular adhesion molecules, including ICAM1, in the brains of AD model mice. Furthermore, they showed that, *in vitro*, soluble Aβ species that have been implicated in AD pathogenesis triggered the conversion of 'inactive' LFA-1 to a high-affinity conformation that promotes neutrophil adhesion to endothelial cells.

These findings suggest that neutrophil invasion of the CNS contributes to the pathogenesis of AD and that blocking this process might have therapeutic potential. The pathways through which neutrophils contribute to neuropathology are unclear, although the authors suggest that the release of cytotoxic substances, such as interleukin-17 or neutrophil extracellular traps (composed of chromatin and proteases) or the promotion of microgliosis might be important.

Katherine Whalley

ORIGINAL RESEARCH PAPER Zenaro, E. *et al.* Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. *Nat. Med.* **21**, 880–886 (2015)
FURTHER READING Heppner, F. L. *et al.* Immune attack: the role of inflammation in Alzheimer disease. *Nat. Rev. Neurosci.* **16**, 358–372 (2015)

> "neutrophils adhered to the endothelial lining of the brain's blood vessels before migrating into and through the parenchyma"

© 2015 Macmillan Publishers Limited. All rights reserved