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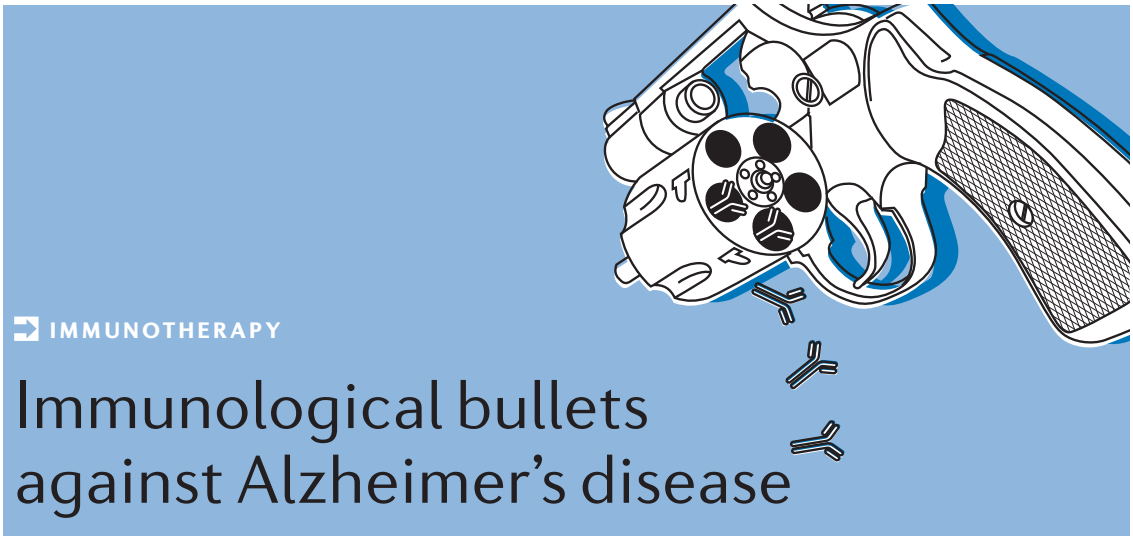

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IMMUNOTHERAPY

Immunological bullets against Alzheimer's disease

Alzheimer's disease is associated with the increased production and accumulation of amyloid-β peptides in the brain. An inflammatory component has also been recognized, although the exact contribution of innate immune signalling to disease pathogenesis is still unclear. Here, vom Berg, Prokop and colleagues identify interleukin-12 (IL-12) and IL-23 signalling as a therapeutic target in this neurodegenerative disorder.

Microglia are brain- and spinal cord-resident cells of myeloid origin, and there has been some debate regarding whether they contribute to the clearance of amyloid-β following their activation. The authors analysed the phenotype of microglia from APP/PS1 transgenic mice, which are used as a model of Alzheimer's disease, and found increased expression of p40 (the common subunit of IL-12 and IL-23) compared with microglia from wild-type mice. So, they crossed APP/PS1 mice with mice that are deficient for p40, p35 (the α-subunit of IL-12) or p19 (the α-subunit of IL-23) to investigate the role of these cytokines in Alzheimer's disease pathogenesis.

Strikingly, these cytokine-knockout APP/PS1 mice showed reduced disease severity compared with APP/PS1 mice, as assessed by the accumulation of amyloid-β in young mice and the formation of amyloid-β plaques in older mice. Moreover, experiments with bone marrow-chimeric mice indicated that microglial cell-derived IL-12 and IL-23 (but not peripheral myeloid cell-derived IL-12 and IL-23) are involved in disease progression.

So, can these findings have a therapeutic application? Intraperitoneal administration of a p40-specific antibody for 11–13 weeks reduced early amyloid-β plaque formation (at 120 days of age) in APP/PS1 mice. Moreover, intracerebroventricular administration of the p40-specific antibody in older APP/PS1 mice ameliorated some behavioural and cognitive deficits. In addition, the concentration of p40 in the cerebrospinal fluid of patients with Alzheimer's disease was shown to correlate with the patients' performance in mental evaluation tests, supporting a role for IL-12 and IL-23 in human disease. These results are promising from a translational perspective given that the safety of p40-specific antibodies has been previously evaluated in clinical trials for the treatment of psoriasis, Crohn's disease and multiple sclerosis.

Finally, gene expression analyses by the authors and others suggest that microglial cell-derived IL-12 and IL-23 may act by modulating the activity of astrocytes, which express the signalling subunit of the IL-12 receptor and the IL-23 receptor. However, further studies are needed to fully understand how IL-12 and IL-23 contribute to Alzheimer's disease pathogenesis.

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> "microglial cell-derived IL-12 and IL-23 ... are involved in disease progression"

ORIGINAL RESEARCH PAPER vom Berg, J. *et al.* Inhibition of IL-12/IL-23 signaling reduces Alzheimer's disease-like pathology and cognitive decline. *Nature Med.* 25 Nov 2012 (doi:10.1038/nm.2965)