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NEUROIMMUNOLOGY

Complement is no bystander in CNS degeneration

Fresh insight into the contribution of the complement pathway to degeneration in the brain has come from two new animal studies. The research shows that knockout of complement C3 protects against neurodegeneration in a model of Alzheimer disease (AD), and identifies a novel mechanism of oligodendrocyte death in neuromyelitis optica (NMO).

The study in AD built on previous work showing that blockade of the complement pathway protects against ageing and early AD in mice. The importance of complement when amyloid-β (Aβ) plaques have accumulated, and the implications for cognitive function, remained unclear. The new study, led by Cynthia Lemere, aimed to address both questions.

The researchers used APP/PS1 mice — a model of AD in which Aβ plaques accumulate with age — and generated animals with an additional knockout of complement C3. They compared the cognitive performance and brain changes of these mice with those of standard APP/PS1 mice, wild-type mice and C3-deficient wild-type mice.

At 16 months of age, the C3-deficient APP/PS1 mice exhibited better cognitive performance than standard APP/PS1 mice. Their performance matched that of the wild-type mice, but not of C3-deficient wild-type mice in all tests, indicating that C3 deficiency mitigates cognitive decline.

Aβ plaque levels in the brains of the C3-knockout APP/PS1 mice were greater than those in the APP/PS1 mice, but altered glial responses to plaques were observed. The morphology of microglia indicated less reactive microgliosis in the C3-knockout APP/PS1, and neither astrocytes nor microglia infiltrated plaques to the same degree. Furthermore, the C3 deficiency prevented synaptic degeneration and age-dependent neuronal loss in the hippocampus.

"Our results suggest that complement signalling plays a glia-mediated role in synaptic and neuronal function in the plaque-rich, aged brain, and that inhibition of complement proteins is a potential therapeutic target for AD treatment," concludes Lemere.

The study in NMO focused on oligodendrocyte injury, a prominent feature of NMO that remains unexplained. Activation of the complement pathway in astrocytes owing to binding of anti-aquaporin 4 antibodies (AQP4-IgG) is central to the pathogenesis of NMO, but AQP4-IgG cannot bind to oligodendrocytes.

"Because of the proximity of oligodendrocytes and astrocytes, and the fact that astrocytes but not oligodendrocytes express the complement inhibitor CD59, we speculated that complement activation by astrocytes could injure nearby oligodendrocytes," explains senior author Alan Verkman.

The researchers first tested their hypothesis in astrocyte and oligodendrocyte co-cultures, exposing the cells to AQP4-IgG and human complement, and assessing cytotoxicity with a dead-cell stain. Oligodendrocyte death was greatest among the cells closest to astrocytes. Immunofluorescence revealed that the complement pathway was activated only in astrocytes, but the membrane attack complex was subsequently deposited on nearby oligodendrocytes, indicating a bystander mechanism of oligodendrocyte death. Experiments in a rat model confirmed the findings *in vivo*.

"Complement bystander injury provides a novel mechanism in NMO pathogenesis that could explain many features of NMO, such as early and prominent demyelination and blood–brain barrier injury," says Verkman.

The researchers now plan to determine the generalizability of their finding to other CNS cell types in NMO, and to investigate therapeutics that block the bystander mechanism.

Ian Fyfe

> "Complement bystander injury provides a novel mechanism in NMO"

ORIGINAL ARTICLES Shi, Q. *et al.* Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Sci. Transl. Med.* **9**, eaaf6295 (2017) | Tradtrantip, L. *et al.* Bystander mechanism for complement-initiated early oligodendrocyte injury in neuromyelitis optica. *Acta Neuropathol.* http://dx.doi.org/10.1007/s00401-017-1734-6 (2017)