MULTIPLE SCLEROSIS

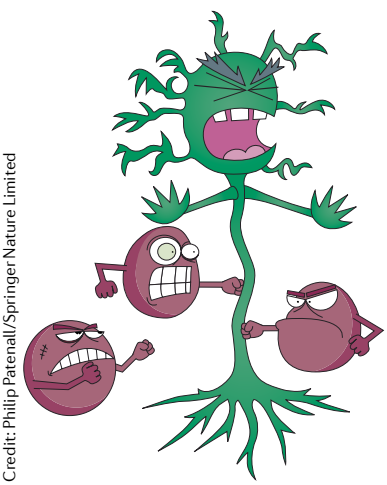
New rat model recapitulates disabling grey matter damage in multiple sclerosis

> Introduction of the β-synuclein-reactive T cells … caused severe neurological disease that differed from traditional EAE

Direct autoimmune attack of the grey matter can lead to the damage that underlies disability in multiple sclerosis (MS), results of a study recently published in *Nature* suggest. In a newly established rat model, immune targeting of β-synuclein — a protein that is present at high levels in neurons — caused grey matter damage and disability.

Although MS is a demyelinating disease, grey matter lesions and atrophy are thought to underlie the accumulation of disability. However, knowledge of the mechanisms that lead to this grey matter damage is limited, partly because the most widely used animal model of MS — experimental autoimmune encephalitis (EAE) — does not recapitulate this aspect of the disease.

"There are numerous EAE models; however, in virtually all models the inflammatory lesions reside within the CNS white matter, and these are mainly located within the spinal cord," explains Alexander Flügel, a senior author of the new study. "Lesions within the grey matter, in particular in brain cortical areas, are virtually absent. My colleagues and I were always puzzled by this limitation and were not satisfied by the hypothesis that T cell-independent disease mechanisms should cause this extensive cortical grey matter damage."



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To probe this problem, Flügel and colleagues went back to the drawing board and designed a different version of EAE in Lewis rats. Rather than using myelin antigens to trigger the condition, as in all existing versions of the model, they developed T cells that were reactive against β-synuclein. This protein is abundant in grey matter and has previously been identified as a possible autoimmune antigen.

Introduction of the β-synuclein-reactive T cells into wild-type rats caused severe neurological disease that differed from traditional EAE. Symptoms included paralysis, stereotypical scratching movements and ataxia.

"This came as a surprise because most neuronal antigens tested beforehand had induced only very weak disease signs, if any," explains Francesca Odoardi, the co-senior author of the study. "The biggest surprise, however, came when we analysed the animals histologically. Almost exclusively, the CNS grey matter was inflamed, in particular the brain cortex."

To confirm that the effects of the T cells were indeed mediated by their reactivity against β-synuclein, the researchers also made a T cell-receptor transgenic rat in which >95% of T cells were reactive against β-synuclein. T cells from these rats caused extensive grey matter lesions, and more than 80% of the transgenic rats developed disease.

To assess the relevance of the animal experiments to humans, Flügel and colleagues also examined reactivity of T cells to β-synuclein in healthy people and individuals with MS. Reactive T cells were observed in both groups, but their levels were higher in people with MS. Interestingly, levels of β-synuclein-reactive T cells were particularly high in people with chronic progressive MS.

"This is the first report that shows that T cell-mediated grey matter autoimmunity can evoke CNS atrophy and irreversible neuronal damage and loss," says Flügel. "It is also the first report that indicates that β-synuclein reactivity of peripheral T cells could be significant in patients with MS."

The researchers say that their model can be used to further study the mechanisms behind immune-mediated grey matter damage in MS. The next stage is to determine how their findings can be translated to benefit patients.

"We do not know when β-synuclein-reactive T cells arise and expand in MS and what functional relevance these have in the disease process, but we believe answers to these questions will provide prognostic and diagnostic measures," says Flügel. "Furthermore, experimental studies might reveal new therapeutic targets through which neuronal damage in MS could be prevented or reduced, thereby stopping or slowing down disease progression in MS."

Ian Fyfe

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