> CSF moved along perivascular spaces and entered the brain via the glymphatic pathway

Mori used dynamic contrast-enhanced MRI to identify where CSF was entering the brain tissue. After MCA occlusion, CSF moved along perivascular spaces and entered the brain via the glymphatic pathway.

"We were surprised that the glymphatic system, which normally helps the brain by removing waste while we sleep, has a darker side after stroke and could actually contribute to the damage," says Humberto Mestre, the first author of the study.

The findings suggest that blocking glymphatic flow would reduce post-stroke oedema, but Nedergaard notes that glymphatic clearance also has beneficial effects: "glymphatic clearance probably plays a role in removing oedema fluid in the days and weeks after an ischaemic insult, so future work should establish a balance between glymphatic inhibition and facilitation to optimize recovery."

Sarah Lemprière

ORIGINAL ARTICLE Mestre, H. et al. Cerebrospinal fluid influx drives acute ischemic tissue swelling. *Science* https://doi.org/10.1126/science.aax7171 (2020)

> vitamin B_3 increased the amount of myelin debris phagocytosed by primary microglia

In vitro, vitamin B_3 increased the amount of myelin debris phagocytosed by primary microglia derived from both young and aged mice, indicating that the treatment could aid remyelination.

Rawji and colleagues injected the demyelinating toxin lysolecithin into the spinal cord of middle-aged (9–12 months old) mice, some of which were treated with vitamin B_3 for 7 days after injection. At 21 days post-injection, lysolecithin-induced lesions in animals that were treated with vitamin B_3 had a greater percentage of remyelinated axons than lesions in mice that received vehicle only.

"This finding is significant for the field as it reveals a novel and relatively safe therapeutic strategy to enhance remyelination", notes Rawji. "We would, therefore, like to carry out a clinical trial of vitamin B_3 in individuals with MS," concludes Yong.

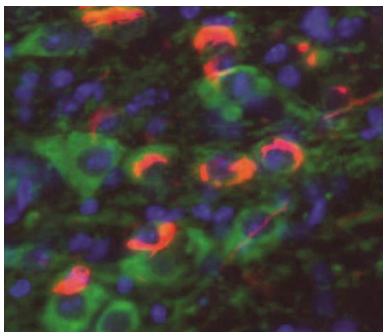
Sarah Lemprière

ORIGINAL ARTICLE Rawji, K. S. et al. Niacin-mediated rejuvenation of macrophage/microglia enhances remyelination of the aging central nervous system. *Acta Neuropathologica* https://doi.org/10.1007/s00401-020-02129-7 (2020)

NEURODEGENERATIVE DISEASE

*APOE*ε4* promotes synucleinopathy

Apolipoprotein E (*APOE*) genotype directly influences the development of α-synuclein pathology in dementia with Lewy bodies (DLB) and Parkinson disease (PD) dementia, two new studies have shown. The findings reinforce the importance of *APOE* as a potential therapeutic target in neurodegenerative disease.



Phosphorylated α-synuclein aggregates (red) accumulated in the substantia nigra of a mouse that expresses *APOE*ε4* after injection of fibrils in the striatum. Image courtesy of Z. M. Wargel and B. M. Freeberg.

The *APOE*ε4* allele is the strongest known genetic risk factor for Alzheimer disease (AD) and is also a prominent genetic risk factor for DLB. DLB pathology is often accompanied by amyloid-β (Aβ) pathology, but whether the link between *APOE*ε4* and DLB can be explained by this pathology has been unclear. Now, two mouse studies have shown that the association is independent of Aβ and explained by direct effects of *APOE* on α-synuclein.

In the first study, two mouse models of α-synuclein pathology — one that is genetically modified to express mutant α-synuclein and another produced by injection of preformed α-synuclein fibrils — were generated in animals with different *APOE* genotypes. "We took advantage of mice that have been genetically engineered to express one of the human forms of *APOE* or mice in which *APOE* is completely knocked out," says Albert Davis, the first author of this study.

In both mouse models of α-synuclein pathology, animals that expressed the *APOE*ε4* allele developed the most severe α-synuclein pathology and died soonest. Mice that expressed the *APOE*ε2* allele developed less severe pathology and lived longest. In one model, mice that expressed *APOE*ε2* developed less severe pathology than the *APOE*-knockout mice. "This finding suggests that *APOE*ε2* may have a protective effect in addition to *APOE*ε4* being detrimental," says Davis.

Davis and colleagues also studied the effect of *APOE* genotype in two independent cohorts of patients with PD. In both cohorts, the *APOE*ε4* allele was associated with faster cognitive decline.

The second research team, led by Na Zhao and Guojun Bu, generated a mouse model of synucleinopathy that lacked Aβ pathology to study the direct effects of *APOE* genotype on α-synuclein pathology. "We generated the animal model by overexpressing human wild-type α-synuclein using adeno-associated, virus-mediated gene delivery to mice expressing human *APOE*ε2*, *APOE*ε3* or *APOE*ε4*," explains Zhao, the first author of the study.

In this mouse model, expression of *APOE*ε4* was associated with more extensive α-synuclein pathology, neurodegeneration and motor and memory dysfunction. Consistent with these findings, analysis of post-mortem brain samples from patients with DLB but minimal Aβ pathology demonstrated that *APOE*ε4* carriers had the most α-synuclein pathology.

"These findings provide insight into the role of *APOE*ε4* in DLB and PD dementia that may guide future clinical trial designs and early prevention strategies that target *APOE* and related pathways," says Bu. Both teams say the focus is now on determining the mechanisms by which *APOE*ε4* promotes α-synuclein pathology.

Ian Fyfe

ORIGINAL ARTICLES Davis, A. et al. *APOE* genotype regulates pathology and disease progression in synucleinopathy. *Sci. Transl. Med.* **12**, eaay3069 (2020) | Zhao, N. et al. APOE4 exacerbates α-synuclein pathology and related toxicity independent of amyloid. *Sci. Transl. Med.* **12**, eaay1809 (2020)
RELATED ARTICLE Yamazaki, Y. et al. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat. Rev. Neurol.* **15**, 501–518 (2019)