ALZHEIMER DISEASE

Astrocytic IL-3 could help microglia protect against Alzheimer disease

Astrocyte-derived IL-3 promotes the clearance of Alzheimer disease (AD)-associated brain pathology by aiding the deployment of phagocytic microglia to amyloid-β (Aβ) plaques, according to new research published in *Nature*. The study, which was led by Cameron McAlpine, Filip Swirski and Rudolph Tanzi, indicates that the IL-3 signalling pathway could be targeted for the treatment of AD.

"The immune system plays a complex and unclear role in the progression of AD," explains McAlpine. "IL-3 is a multifunctional cytokine that has been shown to mediate inflammatory and immune response pathways in other contexts, and we hypothesized that it was a suitable target to explore the diverse roles of the immune system in AD."

First, the researchers examined the effects of knocking out *Il3* — the gene that encodes IL-3 — in wild-type mice and the *5×FAD* mouse model of AD. On an otherwise wild-type genetic background, the knockout did not notably alter brain physiology or cognitive function. However, *Il3* knockout in *5×FAD* mice led to exacerbation of memory impairments and an increased Aβ burden in the cortex.

Further investigations in mice revealed that IL-3 was generated constitutively by a subset of astrocytes in the brain. Histological analysis of post-mortem human brain tissue confirmed colocalization of IL-3 with astrocytic markers.

In wild-type mice, microglial expression of the IL-3 receptor IL-3Rα was found to increase with age. Intriguingly, upregulation of IL-3Rα in microglia began at a much younger age in *5×FAD* mice than in wild-type mice, suggesting that these cells were being primed to respond to IL-3 early in the course of AD.

The researchers also showed that the presence of IL-3 influenced the morphology and distribution of microglia in *5×FAD* mice. In $Il3^{+/+}$ *5×FAD* animals, the microglia were globular in appearance, indicating an activated state, and tended to cluster around Aβ plaques. A similar phenomenon was observed in post-mortem brain tissue from patients with AD. By contrast, in $Il3^{-/-}$ *5×FAD* mice, the microglia had a ramified morphology, typical of a 'resting' phenotype, and were more uniformly distributed throughout the brain.

"Our data suggest that in the absence of IL-3, microglia do not recognize or react to the build-up of Aβ," says McAlpine. "IL-3 signalling licenses microglia to recognize AD pathology and clear Aβ."

"In addition to promoting microglial clearance of Aβ, IL-3 may subsequently quell neuroinflammation, a major killer of neurons in AD," adds Tanzi.

"The specific communication between astrocytes and microglia that we have uncovered is perhaps most significant," comments Swirski. "I was especially struck by how IL-3 helps microglia cluster around Aβ plaques."

The investigators also explored the therapeutic potential of IL-3 in *5×FAD* mice. In these animals, continuous infusion of recombinant IL-3 into the lateral ventricle over a 28-day period led to increased clustering of microglia around Aβ deposits, a reduced Aβ load in the brain and improvements in memory.

"Although much work is still needed, we hypothesize that targeting IL-3 might reduce AD-related pathology," concludes McAlpine. "It is also conceivable that IL-3 has important roles in other neurological diseases and in healthy ageing, and these are topics that our group is actively investigating."

Heather Wood

ORIGINAL ARTICLE McAlpine, C. S. et al. Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. *Nature* https://doi.org/10.1038/s41586-021-03734-6 (2021)
RELATED ARTICLE Barron, J. J. & Molofsky, A. V. A protective signal between the brain's supporting cells in Alzheimer's disease. *Nature* https://doi.org/10.1038/d41586-021-01870-7 (2021)

IN BRIEF

NEUROMUSCULAR DISEASE

Drug repurposing shows promise for Charcot–Marie–Tooth disease

The antibiotic florfenicol can prevent the development of symptoms in a mouse model of Charcot–Marie–Tooth disease, new research demonstrates. Some forms of the disease are caused by mutations in *GDAP1*, which is important for mitochondrial function, so the researchers performed an in vitro screen of 1,018 FDA-approved drugs to identify activators of mitochondrial respiration. Florfenicol, which was identified in the screen, ameliorated the development of motor deficiencies when given to pre-symptomatic *Gdap1*-null mice.

ORIGINAL ARTICLE Nuevo-Tapioles, C. et al. Effective therapeutic strategies in a pre-clinical mouse model of Charcot–Marie–tooth disease. *Hum. Mol. Genet.* https://doi.org/10.1093/hmg/ddab207 (2021)

COVID-19

Multiple sclerosis treatment blunts SARS-CoV-2 antibody response

Anti-CD20 treatment for multiple sclerosis (MS) blunts the post-COVID-19 humoral immune response, according to new research. The multicentre observational study included 474 patients with MS and related conditions who had a diagnosis of COVID-19. Of the patients not on anti-CD20 treatment, 85% were positive for SARS-CoV-2 antibodies, compared with just 39.5% of patients on anti-CD20 treatment. This statistically significant difference ($P < 0.0001$) has implications for natural and vaccine-mediated immunity in patients receiving anti-CD20 treatment for MS.

ORIGINAL ARTICLE Klineova, S. et al. Outcomes of COVID-19 infection in multiple sclerosis and related conditions: one-year pandemic experience of the multicenter New York COVID-19 Neuroimmunology Consortium (NYCNIC). *Mult. Scler. Relat. Disord.* https://doi.org/10.1016/j.msard.2021.103153 (2021)

STROKE

A brain implant decodes speech

Machine learning can be used to decode speech from cortical activity recordings in real time, according to a recent study. Researchers implanted a subdural multi-electrode array over the area of cortex that controls speech in an individual with anarthria caused by brainstem stroke. Cortical activity was recorded for a total of 22 h while the participant attempted to say a predefined set of 50 words. Deep learning was applied to this dataset to build computational models that were able to detect and classify the intended words in real time, suggesting that technology has the potential to restore communication in individuals who are paralysed and cannot speak.

ORIGINAL ARTICLE Moses, D. A. et al. Neuroprosthesis for decoding speech in a paralyzed person with anarthria. *N. Engl. J. Med.* **385**, 217–227 (2021)

MIGRAINE

Brain activity altered in visual snow syndrome

A recently published functional MRI study has identified a specific pattern of increased regional cerebral blood flow in individuals with visual snow syndrome compared with healthy controls. The increase was observed over an extensive brain network, mostly comprising areas involved in complex sensory processing, and was present both at rest and when participants viewed a 'snow-like' visual stimulus. The data point to an underlying neurobiological disturbance in visual snow syndrome.

ORIGINAL ARTICLE Puledda, F. et al. Localised increase in regional cerebral perfusion in patients with visual snow syndrome: a pseudo-continuous arterial spin labelling study. *J. Neurol. Neurosurg. Psychiatry* https://doi.org/10.1136/jnnp-2020-325881 (2021)