IN BRIEF

TRAUMATIC BRAIN INJURY

Interneuron transplants elicit hippocampal repair after traumatic brain injury in mice

Interneuron progenitor cells transplanted into the hippocampus can be incorporated into neuronal circuits and improve outcomes after traumatic brain injury (TBI) in a mouse model, according to new research published in *Nature Communications*. Bingyao Zhu and colleagues isolated inhibitory interneuron progenitors from the medial ganglionic eminence of mouse embryos and transplanted these cells into the hippocampus in mice that had been subjected to controlled cortical impact — a mechanical model that is thought to accurately replicate the effects of TBI in humans. The cells were shown to undergo maturation and integrate functionally into hippocampal circuits. The mice that received the transplants showed improvements in memory precision and reductions in post-traumatic seizures, indicating restoration of inhibitory network function in the hippocampus.

ORIGINAL ARTICLE Zhu, B. et al. Transplanted interneurons improve memory precision after traumatic brain injury. *Nat. Commun.* **10**, 5156 (2019)

NEUROMUSCULAR DISEASE

Cladribine shows promise in patients with difficult-to-treat myasthenia gravis

A new open-label study published in the *European Journal of Neurology* has provided evidence of efficacy of cladribine in difficult-to-treat cases of myasthenia gravis (MG) — a rare autoimmune neuromuscular disorder. Cladribine is an immunomodulatory drug that has been approved in some countries for the treatment of relapsing–remitting multiple sclerosis. The study included 13 patients with MG who had shown an insufficient response to standard therapy for this condition. Following 6 months of treatment with cladribine, 11 of the participants demonstrated significant clinical improvement, defined as a reduction of ≥3 points on the Myasthenia Gravis Composite scale. The investigators conclude that cladribine is a promising treatment for MG but additional studies are needed to refine the dosing regime and to determine long-term efficacy and safety.

ORIGINAL ARTICLE Rejdak, K. et al. Cladribine in myasthenia gravis: a pilot open-label study. *Eur. J. Neurol.* https://doi.org/10.1111/ene.14124 (2019)

ALZHEIMER DISEASE

A single case from Colombia provides insights into Alzheimer disease resistance

The autosomal dominant presenilin 1 (*PSEN1*) E280A mutation is strongly linked to early-onset Alzheimer disease (AD), with carriers typically developing mild cognitive impairment (MCI), rapidly progressing to dementia, before the age of 50 years. However, as recently reported in *Nature Medicine*, a woman from Colombia with this mutation did not develop MCI until she was in her seventies, despite having a high amyloid-β burden in her brain. The resistance to AD in this individual was attributed to homozygosity for the R136S mutation in the ε3 allele of apolipoprotein E (*APOE*), also known as the Christchurch or *APOE3ch* mutation. The beneficial effects of *APOE3ch* seemed to be mediated through limitation of tau pathology and neurodegeneration. On the basis of these findings, the authors suggested a possible role for APOE modulation in the prevention and treatment of AD.

ORIGINAL ARTICLE Arboleda-Velasquez, J. F. et al. Resistance to autosomal dominant Alzheimer's disease in an *APOE3* Christchurch homozygote: a case report. *Nat. Med.* **25**, 1680–1683 (2019)

DEMENTIA

High-salt diet promotes Alzheimer disease-like changes

A high-salt diet leads to the development of hallmark Alzheimer disease (AD) pathology and cognitive impairment in mice, according to new research published in *Nature*. The study reveals previously unknown molecular mechanisms that could have therapeutic implications.

In previous work, a high-salt diet in mice led to cerebral endothelial dysfunction, a 25% reduction in cerebral blood flow, and associated cognitive decline. The cognitive impairment was related to a deficit of endothelial nitric oxide, but the exact causal mechanisms remained unclear.

"The 25% reduction in cerebral blood flow did not seem sufficiently severe to cause cognitive impairment, as two cups of coffee reduce resting cerebral blood flow by 30% in humans," explains Costantino Iadecola, one of the lead investigators of the new study. "Therefore, we looked for alternative explanations."

The researchers focused on tau, a protein that is involved in AD pathology and has previously been associated with endothelial dysfunction and cognitive impairment. They fed a high-salt diet to mice from the age of 8 weeks and assessed levels of phosphorylated tau — the form of the protein that aggregates in AD — in the brain over time. The high-salt diet was associated with increased levels of phosphorylated tau in the brain. After 12 weeks on the high-salt diet, animals began to develop impairments in object recognition and on spatial memory tests.

Further investigation provided greater insight into the molecular mechanisms, revealing that the nitric oxide deficit previously

CEREBROVASCULAR DISEASE

Global small vessel disease brain changes predict cognitive decline

A measure derived from multiple pathologies associated with cerebral small vessel disease (SVD) predicts long-term cognitive decline, according to research published recently in *Stroke*. The MRI-based measure provides a new way to assess the effects of changes caused by SVD.

Cerebral SVD is characterized by several features that can be detected with MRI, including white matter hyperintensities (WMHs), small subcortical infarcts, lacunes, enlarged perivascular spaces, microbleeds and brain atrophy. However, no standard method has been developed to assess how these features influence the course of the disease. In their study, Hanna Jokinen and colleagues developed a novel approach.

The researchers analysed the brains of 560 individuals from the Leukoaraiosis and Disability Study by use of automated MRI segmentation methods based on convolutional neural networks and brain atlases. These methods were used to determine the volume of each SVD-associated brain change. Patients were then monitored with tests of cognitive function and activities of daily living for up to 7 years, and the scores were analysed alongside the MRI data to identify associations between SVD-related pathology and cognitive decline.

Linear mixed model analysis showed that the volumes of WMHs, lacunes, cerebral grey matter and the hippocampus were independent predictors of cognitive decline. Furthermore, a quantitative global score derived from all four measures was a better predictor of cognitive decline than any of the individual MRI measures alone.

"Global quantification of SVD-related brain changes provides a comprehensive neuroimaging metric associated with vascular cognitive impairment and may