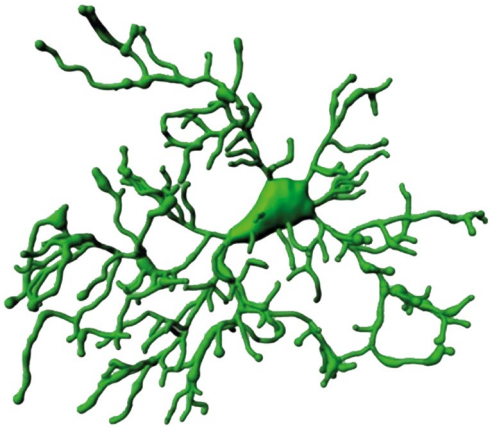
ALZHEIMER DISEASE

Microglia, spreaders of Aβ seeds

Microglia could have an important role in the propagation of amyloid-β (Aβ) pathology, according to new research published in *Nature Neuroscience*. The findings add a new dimension to the involvement of microglia in Alzheimer disease (AD) and indicate a potential new therapeutic target.



3D reconstruction of a microglial cell inside a neuronal graft. Copyright SpringerNature Ltd.

Aβ pathology is known to propagate through the brain via a prion-like mechanism, whereby misfolded Aβ acts as 'seeds' to initiate further misfolding. The way in which Aβ seeds are transferred between cells, however, remains unclear. In their new study, Paolo d'Errico, Melanie Meyer-Luehmann and colleagues followed their suspicions about one possibility.

"Owing to the evident role of microglia in spreading pathological proteins such as tau, we decided to study whether this cell type can act as a cellular transporter for Aβ as well," says Meyer-Luehmann.

Meyer-Luehmann herself first demonstrated that propagation of AD pathology could be studied with a grafting method in mice. In this procedure, healthy neurons from wild-type mice are grafted into the brains of AD model mice. Aβ pathology spreads to the grafted neurons, leading to their degeneration. The new study was based on the same approach.

In this work, the researchers grafted wild-type neurons into the brains of 5×FAD mice, which develop Aβ pathology. The mice were further engineered to express green fluorescent protein in microglia. By 2 weeks after the transplantation procedure, microglia from the graft recipients had migrated into the grafts. The team then investigated whether these microglia could be taking Aβ with them.

They first exploited the fact that the phagocytic capability of microglia diminishes with age, and assessed whether the development of Aβ pathology in the graft differed between old and young mice. Aβ burden in the graft was much lower in older mice than in younger mice, indicating that microglia do transport Aβ and that this process becomes less efficient with age. Furthermore, in 5×FAD mice with impairments in microglial function, Aβ deposition in the graft was less extensive than in mice with normal microglial function.

"Our study sheds new light on the involvement of microglia in the propagation of Aβ pathology from a diseased to a healthy region," says d'Errico. "Microglia are known to have both beneficial and detrimental roles in AD, but the role of microglia in transporting Aβ from one region to another has never been described before."

The researchers say their technique could be used to investigate other factors that influence Aβ propagation and to study other neurodegenerative diseases. However, their findings could also have more direct implications for patients: "We think our study could help to develop therapies that have microglia as a potential therapeutic target," says d'Errico.

Ian Fyfe

ORIGINAL ARTICLE d'Errico, P. et al. Microglia contribute to the propagation of Aβ into unaffected brain tissue. *Nat. Neurosci.* https://doi.org/10.1038/s41593-021-00951-0 (2022)
RELATED ARTICLE Leng, F. & Edison, P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat. Rev. Neurol.* **17**, 157–172 (2021)

IN BRIEF

HUNTINGTON DISEASE

A machine learning model of HD progression

The progression of Huntington disease (HD) involves nine disease states of increasing severity, according to a study published in *Movement Disorders*. Researchers integrated data on motor, cognitive and functional measures from four existing studies and used machine learning to develop a model of disease progression. States 1 and 2 occurred before motor diagnosis and lasted about 16 years. States 3–5 were described as transition states and lasted a total of around 10 years. States 6–9, the 'late-disease' states, also lasted about 10 years. The findings could improve clinical trial design and participant selection.

ORIGINAL ARTICLE Mohan, A. M. et al. A machine-learning derived Huntington's disease progression model: insights for clinical trial design. *Mov. Dis.* https://doi.org/10.1002/mds.28866 (2021)

STROKE

Change in stroke outcomes over 20 years

Functional outcomes for individuals with ischaemic stroke in Japan improved over the past 20 years, says new research published in *JAMA Neurology*. The study included 183,000 participants who had acute stroke between January 2000 and December 2019. For participants with intracerebral haemorrhage, the proportion with favourable outcomes decreased over time; however, the proportion of favourable outcomes increased among participants with ischaemic stroke. Further analysis indicated that this disparity reflected the introduction of reperfusion therapy for ischaemic stroke.

ORIGINAL ARTICLE Toyoda, K. et al. Twenty-year change in severity and outcome of ischemic and hemorrhagic strokes. *JAMA Neurol.* https://doi.org/10.1001/jamaneurol.2021.4346 (2021)

EPILEPSY

High rate of epilepsy in young individuals who died with COVID-19

Epilepsy is over-represented among young individuals who died from COVID-19 in Hungary, according to data published in *Seizure*. Researchers analysed data for 11,686 individuals who died from COVID-19 in Hungary and found that 2.2% had epilepsy. Of those individuals who died under the age of 50 years, 9.3% had epilepsy. The median prevalence of epilepsy in Europe is 0.52%, indicating an over-representation of epilepsy among those who died from COVID-19. However, the authors acknowledge the absence of Hungarian epidemiological data on epilepsy as a limitation of their work.

ORIGINAL ARTICLE Horváth, R. A. et al. Epilepsy is overrepresented among young people who died from COVID-19: analysis of nationwide mortality data in Hungary. *Seizure* https://doi.org/10.1016/j.seizure.2021.11.013 (2021)

PARKINSON DISEASE

Exosomal microRNA is promising biomarker in PD

Distinguishing between Parkinson disease (PD) and progressive supranuclear palsy (PSP) on the basis of clinical features can be challenging, but new research suggests that exosomal microRNAs (miRNAs) can act as biomarkers to differentiate between the two disorders. Researchers analysed levels of 188 miRNAs in serum from individuals with PD or PSP and healthy control participants. The levels of a set of six exosomal miRNAs discriminated PSP from PD with a sensitivity of 0.89 and a specificity of 0.90, indicating potential utility as a biomarker.

ORIGINAL ARTICLE Manna, I. et al. Exosomal miRNA as peripheral biomarkers in Parkinson's disease and progressive supranuclear palsy: a pilot study. *Parkinsonism Relat. Disord.* https://doi.org/10.1016/j.parkreldis.2021.11.020 (2021)