

 COVID-19

Inflammation links mild COVID-19 with long-term cognitive impairment

Mild COVID-19 can have long-term effects on the brain via neuroinflammatory mechanisms, according to new research published in *Cell*. The findings provide therapeutic targets for future work.

After COVID-19, some people have long-term neurological symptoms that are similar to those of cancer therapy-related cognitive impairment (CRCI). Neuroinflammatory processes are key to CRCI pathophysiology, so the aim of the new study was to assess these processes in COVID-19.

“Moderate-to-severe and systemic SARS-CoV-2 infection can affect the brain in several ways — including vasculopathy and direct infection — but we set out to test the effects of mild respiratory infection alone on the brain,” explains Michelle Monje, who led the study with Akiko Iwasaki.

SARS-CoV-2 enters cells via the human ACE receptor (hACE), so the researchers limited the location of the infection in mice by selectively inducing expression of hACE in the respiratory tract. Mice received either

intranasal SARS-CoV-2 or mock infection, and cerebrospinal fluid (CSF) samples were taken either 7 days or 7 weeks after infection to assess inflammatory markers.

Compared with uninfected mice, infected mice had higher CSF levels of multiple cytokines and chemokines, as well as increased microglial activation in subcortical and hippocampal white matter. Neuron generation in the hippocampus and the amount of myelin in the subcortical white matter were also both lower in infected mice than in uninfected mice.

“These findings point to the possibility that the infection does not need to happen directly within the brain to cause long-term damage,” says Iwasaki. The researchers now plan to test therapies being developed for CRCI in preclinical models of COVID-19-related cognitive impairment as a step towards clinical trials.

Sarah Lemprière

ORIGINAL ARTICLE Fernández-Castañeda, A. et al. Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. *Cell* <https://doi.org/10.1016/j.cell.2022.06.008> (2022)

 MULTIPLE SCLEROSIS

Insights into the molecular pathways of progressive multiple sclerosis

Molecular pathways involved in early neurodegeneration in progressive multiple sclerosis (MS) have been identified using a novel tissue analysis technique. The work, published in *Nature Neuroscience*, identifies potential therapeutic targets.

Neurodegeneration underlies progression in MS, but incomplete understanding of the mechanisms involved is hampering the development of effective therapies. In their new work, Lars Fugger and colleagues used spatial transcriptomics to gain insight into the specific pathways involved.

“Spatial transcriptomics is a novel technique that can detect the expression of thousands of genes with spatial resolution directly in the tissue,” explains Fugger. “Thus, it becomes possible to combine the structural detail of microscopy with high-dimensional measurements to capture complex disease pathways.”

The researchers studied post-mortem tissue from 13 patients with progressive MS and five control individuals. They first

mapped areas of neurodegeneration in the grey matter and identified regions at different stages of degeneration. They then analysed changes in gene and protein expression in these areas to determine which molecular pathways are associated with different stages.

“By measuring gene expression and localization in the tissue simultaneously, we were able to identify receptor–ligand pairs in close proximity to one another in specific stages of MS neurodegeneration in the brain, suggesting that the corresponding signalling could be involved in the disease,” explains Fugger.

Crucially, the approach identified pathways involved in early neurodegeneration, when treatment is most likely to be beneficial. These pathways, therefore, represent candidates for therapeutic targeting.

Ian Fyfe

ORIGINAL ARTICLE Kaufmann, M. et al. Identification of early neurodegenerative pathways in progressive multiple sclerosis. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-022-01097-3> (2022)

 ALZHEIMER DISEASE

Restoring synapses in AD models

A new study published in *Science Translational Medicine* has shown that a silent allosteric modulator of metabotropic glutamate receptor 5 (mGluR5) can reverse synapse loss in mouse models of Alzheimer disease (AD). The treatment was found to reverse AD-associated changes in gene expression and to prevent complement component C1Q from tagging synapses for subsequent engulfment by glial cells.

“Both amyloid- β (A β) and inflammation have been implicated in synapse loss, which is directly tied to symptoms in AD,” explains Stephen Strittmatter, who led the study with Jason Cai. “We had previously shown that prion protein and mGluR5 mediate the effects of A β , and we sought to understand how mGluR5 is related to inflammatory effects on synapses and how it might be targeted.”

The researchers used two mouse models of AD known as APP/PS1 and dKI. Synapses in the brain were visualized using ¹⁸F-SynVesT-1 PET, which detects synaptic vesicle glycoprotein 2A (SV2A). Before treatment with the mGluR5 silent allosteric modulator BMS-984923, the mice were allowed to age to a point at which synaptic density was substantially reduced in comparison with wild-type animals of the same age.

A 1-month course of oral treatment with BMS-984923 restored synaptic density in these mice to wild-type levels, and single-nucleus transcriptomic analysis revealed normalization of neuronal gene expression signatures. Further experiments in dKI mice indicated that BMS-984923 prevented C1Q from localizing to synapses, as indicated by a reduction in co-localization of C1Q with the synaptic marker PSD95.

A clinical trial has now been initiated to test the safety, tolerability and pharmacokinetics of BMS-984923 in healthy individuals. In addition, Cai highlights potential future applications of the synaptic imaging approach that was used in the study. “I believe that SV2A PET could be adopted in preclinical trials of other AD drugs and as an end point in future clinical trials,” he comments. “My laboratory is currently applying this imaging approach in a rat AD model to measure synapse dynamics at a very early stage of neuropathology.”

Heather Wood

ORIGINAL ARTICLE Spurrier, J. et al. Reversal of synapse loss in Alzheimer mouse models by targeting mGluR5 to prevent synaptic tagging by C1Q. *Sci. Transl. Med.* **14**, eabi8593 (2022)