NEURODEGENERATIVE DISEASE

Mind the liver

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Apolipoprotein E (ApoE) is a lipid transport protein that has been associated with Alzheimer's disease (AD). Among its multiple isoforms, *APOE* ε4 holds the strongest risk factor for sporadic late onset of AD and other dementias. However, little is known about why *APOE* ε4 promotes neurodegeneration. Using humanized-liver mice, a new study uncovers a link between liver-derived *APOE* ε4 and AD pathology.

"We have previously found that *APOE4*-carriers exhibit lower levels of plasma ApoE – mainly derived from the liver – compared to non-carriers, and although plasma ApoE appears not to cross the blood-brain-barrier we also found that plasma ApoE levels were correlated to AD biomarkers in cerebral spinal fluid and cognition; so we speculated that the liver and its processes may be implicated in the risk of neurodegeneration," explains lead investigator Henrietta Nielsen.

APOE is polymorphic in humans but not in other mammals, including laboratory rodents. Although *APOE*-targeted replacement and transgenic mice have been developed, translating results from rodent studies to the human situation remains challenging. Here, the investigators used humanized-liver mice transplanted with primary human hepatocytes derived from *APOE* ε2/ε3 or *APOE* ε4/ε4 donors to study a potential relationship between hepatic ApoE and pathological processes in the brain. "ApoE would work in a human-like environment; human ApoE would only be produced in the peripheral system, by the liver, while the mouse retains its murine ApoE in the central nervous system," highlights Nielsen.

The results show that *APOE* ε4/ε4 liver mice had lower mouse ApoE levels than *APOE* ε2/ε3 liver mice in certain brain areas, which was associated with alterations in synaptic integrity, neuroinflammation and brain insulin signaling. "The most important aspect of our study is that it highlights a role of the liver in different processes in the brain," says Nielsen. The findings also suggest that certain areas in the brain, such as the hippocampus and cerebral cortex, might be more susceptible to neurodegeneration than others, highlighting the importance of studying multiple brain region in AD studies.

Currently, Nielsen's group is working on further characterizing hepatocytes from different *APOE* genotypes and will follow up with more studies on humanized-liver mice. "In the long run, we hope that identification of a risky liver *APOE4* phenotype would promote the development of liver-targeted AD risk-lowering or risk-elimination strategies, which would be easier to implement rather than designing therapies to cross the blood-brain-barrier" concludes Nielsen.

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