NEURODEGENERATIVE DISEASE

*APOE*ε4* links exosomes to cognitive decline

Carriers of the *APOE*ε4* allele have impaired exosome production in the brain that could underlie cognitive decline, according to a new study. The findings present opportunities for novel therapeutic approaches to neurodegenerative disease.

The endosomal–exosomal–lysosomal pathway is involved in neurodegeneration, and several studies have indicated that Alzheimer disease (AD) and the *APOE*ε4* allele are associated with endosomal and lysosomal changes. In the new study, Efrat Levy, Paul Mathews and colleagues built on these previous findings and focused on the role of exosomes, the other component of the pathway.

"We sought to determine whether *APOE*ε4* alters the exosomal pathway and whether there might be pathological linkage between the previously reported endosomal alterations and exosomal pathway changes," explains Levy.

Using post-mortem tissue from people aged 46–98 years, the researchers compared brain exosome levels in heterozygous or homozygous *APOE*ε4* carriers with those in people homozygous for *APOE*ε3*. The *APOE*ε4* allele was associated with lower levels of exosomes than the *APOE*ε3* allele. The same was seen in mice that expressed humanized *APOE* alleles. In the mice, exosome levels did not differ with genotype at 6 months of age, but did at 12 months, indicating an age-dependent effect of *APOE*ε4*.

Regulators of intracellular exosome formation were downregulated in mice that carried *APOE*ε4*, demonstrating that impairment of exosome biogenesis caused the lower exosome levels. In addition, extracellular vesicle membranes in *APOE*ε4* carriers contained higher levels of cholesterol and ceramide than those in non-carriers.

> "the findings suggest that impairments in exosome production cause endosomal and lysosomal deficits"

The results fit with previous findings of endosomal changes in the same mice aged 18 months. "We propose that compromised exosome production in *APOE*ε4*-expressing individuals contributes to pathogenic alterations in endosomal compartments," says Mathews.

Together, the findings suggest that impairments in exosome production cause endosomal and lysosomal deficits that interfere with protein processing in neurons.

"Our study provides a novel mechanism to explain the cognitive decline that occurs independently of AD pathology in *APOE*ε4* carriers," says Levy. "We identify a direction for therapeutic strategies to restore the integrity of the endosomal and exosomal pathways, minimizing the neurodegenerative consequences of diseases such as AD."

Ian Fyfe

ORIGINAL ARTICLE Peng, K. Y. et al. Apolipoprotein E4 genotype compromises brain exosome production. *Brain* https://doi.org/10.1093/brain/awy289 (2018)

ALZHEIMER DISEASE

Amyloid-β 'seeds' found in archived vials of growth hormone

Amyloid-β (Aβ) peptide with the capacity to seed brain amyloid deposition has been detected in archived vials of human cadaveric pituitary-derived growth hormone (c-hGH), a new paper in *Nature* reports. This discovery could explain why some patients who were treated with c-hGH developed Aβ pathology at a young age, despite a lack of genetic risk factors for diseases characterized by Aβ aggregation, such as Alzheimer disease (AD) and cerebral amyloid angiopathy (CAA).

Credit: Esben Klinker Hansen/Alamy Stock Photo

Between 1958 and 1985, 1,883 individuals in the UK received c-hGH to treat growth deficiency. At least 80 of the treated individuals subsequently developed Creutzfeldt–Jakob disease (CJD), which was attributed to contamination of the hormone preparation by pathogenic prion proteins. At autopsy, a number of affected individuals were additionally found to have Aβ pathology in the brain.

A team led by John Collinge at the UCL Institute of Prion Diseases, London, UK, obtained vials of c-hGH from the batches that were used in the patients who developed CJD. Biochemical analysis confirmed that these vials contained potentially pathogenic Aβ peptides.

> "the c-hGH-injected mice acquired a greater burden of Aβ deposits and CAA in the brain"

Next, the researchers injected c-hGH from these batches into the brains of $APP^{NL\text{-}F/NL\text{-}F}$ knock-in mice, which express a humanized form of amyloid precursor protein and usually begin to develop Aβ pathology at ~6 months of age. Compared with control $APP^{NL\text{-}F/NL\text{-}F}$ mice that received phosphate buffered saline injections, the c-hGH-injected mice acquired a greater burden of Aβ deposits and CAA in the brain, implying that the hormone preparation contained Aβ seeding activity.

Collinge and colleagues emphasize that these findings do not suggest that AD is contagious. Nevertheless, as they write in the paper, "it will be important to consider introducing improved methods for removing proteopathic seeds from surgical instruments on a precautionary basis."

Heather Wood

ORIGINAL ARTICLE Purro, S. A. et al. Transmission of amyloid-β protein pathology from cadaveric pituitary growth hormone. *Nature* **564**, 415–419 (2018)
FURTHER READING Jaunmuktane, Z. et al. Evidence for human transmission of amyloid-β pathology and cerebral amyloid angiopathy. *Nature* **525**, 247–250 (2015)