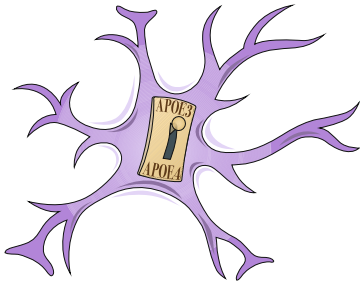


Credit: Phillip Patenall/Macmillan Publishers Limited

and accumulation of cholesterol in astrocytes, and impaired phagocytosis by microglia-like cells.

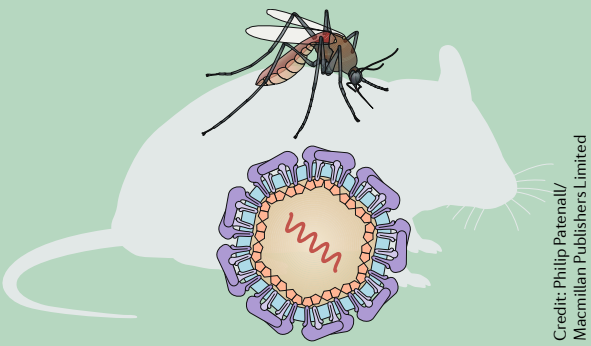
Interestingly, the switch from *APOE*ε3* to *ε4* in iPSCs from healthy individuals was sufficient to cause Aβ accumulation and tau phosphorylation in organoids generated from these cells. By contrast, conversion of *APOE*ε4* to *ε3* in cells from patients with sporadic AD diminished AD-related phenotypes in organoids produced from these cells.

"The action of APOE4 is complicated," comments Tsai. "It impacts many different cell types to facilitate the development of AD pathology. This information is important for future efforts to develop therapeutic interventions."

Charlotte Ridler

> "Surprisingly, a switch from APOE3 to APOE4 had a dramatic impact on the transcriptome of neurons and glial cells"

ORIGINAL ARTICLE Yuan-Ta, L. et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. *Neuron* https://doi.org/10.1016/j.neuron.2018.05.008 (2018)



Credit: Phillip Patenall/ Macmillan Publishers Limited

"We showed that blocking the action of one of the main mediators of neuroinflammation, TNF, with an FDA-approved drug was effective in preventing some of the late neurological outcomes of ZIKV infection," concludes Clarke. "Further studies should confirm the efficacy of TNF blockade in other animal models and in ZIKV-exposed humans so that the treatment can be applied in future ZIKV outbreaks worldwide."

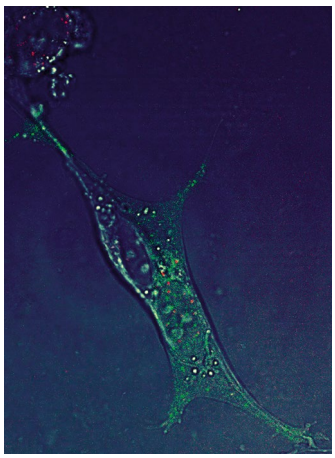
Heather Wood

> "replication of ZKIV was detected in the brain beyond the acute phase of infection"

ORIGINAL ARTICLE Nem de Oliveira Souza, I. et al. Acute and chronic neurological consequences of early-life Zika virus infection in mice. *Sci. Transl Med.* **10**, eaar2749 (2018)

ALZHEIMER DISEASE

Exosomes can spread toxic AD pathology



Credit: A cultured human neuronal cell that has taken up exosomes from Alzheimer disease brain tissue. Exosomes (green) and amyloid-β oligomers (red) colocalize (yellow). Image courtesy of M. Hallbeck.

Exosomes can mediate cell-to-cell propagation of toxic amyloid-β (Aβ) pathology in Alzheimer disease (AD), according to a new study published in *Acta Neuropathologica*. Furthermore, investigators were able to block this exosome-mediated propagation, which suggests that the mechanism is a novel therapeutic target in AD.

Previous work has demonstrated that Aβ pathology can be propagated from cell to cell in a prion-like manner. However, the mechanism by which Aβ is transferred between cells is not known. In their new study, Martin Hallbeck and colleagues investigated whether exosomes have a role in the transfer of toxic Aβ oligomers (oAβ).

"Exosomes are made from endosomes and we knew from our earlier research that intracellular toxic aggregates of Aβ often end up in the endosomal system," explains Hallbeck. "From this, we speculated that the aggregates could end up in exosomes and thus hitch a ride to the next cell."

To test their hypothesis, the researchers first analysed the cellular localization of oAβ in post-mortem brain samples from four patients who had AD. They established that oAβ colocalized with exosomes. Furthermore, the concentration of oAβ associated with exosomes from patients with AD was higher than that from individuals who did not have neurological disease.

To determine whether exosomes could transfer oAβ between cells, the researchers isolated exosomes from the post-mortem tissue of patients with AD and applied them to cells in culture. "Not only were they taken up by the cells, but those cells also propagated the exosomes and their load of oAβ to a further set of co-cultured cells," explains Hallbeck. "This also caused toxicity to the neuronal cells."

The demonstration that toxic oAβ could be propagated by exosomes raised the question of whether this propagation could be stopped. Hallbeck and colleagues tested whether they could either prevent exosomes and their toxic cargo getting out of cells, or block them from getting in.

"Excitingly, inhibition of the formation and release of exosomes by siRNA as well as using an inhibitor of the uptake mechanism for exosomes could stop the spread of exosomes, oligomers and toxicity," says Hallbeck.

The findings could have several implications for research into the management of AD. The researchers say that the differences seen between exosomes from patients with AD and those from control individuals mean that oAβ-containing exosomes could be used as biomarkers of disease, although further work is needed to confirm this possibility. Perhaps most exciting, however, is the possibility of new therapeutic approaches.

"This work and some other studies looking at potential receptors for aggregated protein forms suggest that these mechanisms behind disease propagation could be explored as new drug targets," concludes Hallbeck.

Ian Fyfe

ORIGINAL ARTICLE Sinha, M. S. et al. Alzheimer's disease pathology propagation by exosomes containing toxic amyloid-beta oligomers. *Acta Neuropathol.* https://doi.org/10.1007/s00401-018-1868-1 (2018)