Alzheimer disease

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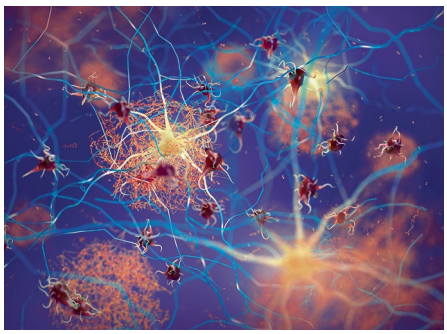
ApoE attracts microglia to amyloid-β plaques



The cell adhesion molecule VCAM1 directs microglia towards ApoE-associated amyloid-β (Aβ) plaques, leading to Aβ clearance, according to new research published in *Nature Aging*. The results of the study highlight this signalling pathway as a potential therapeutic target for Alzheimer disease (AD).

In AD, interleukin-33 (IL-33) induces a change in the functional state of microglia from chemotaxis to phagocytosis, following which microglia migrate towards Aβ and remove plaques. This transition is triggered by surface receptors on the microglia that bind specific ligands associated with Aβ plaques. In the new study, Nancy Ip and colleagues aimed to identify the receptors and ligands involved in regulating this interaction.

Using single-cell RNA sequencing of microglia from APP/PS1 mice (a model of AD), the researchers profiled transcriptional changes during the transition of microglia in response to IL-33. The results demonstrated a sequential transition from a homeostatic state to chemotactic then phagocytic states.

"Through this analysis, we discovered subpopulations of microglia that exhibited chemotactic behaviour, which was crucial in identifying the surface target responsible for sensing and clearing Aβ plaques in AD," explained Ip.

Ip and colleagues identified *Vcam1* expression as a key characteristic of chemotactic microglia. Inhibition of VCAM1, by either genetic ablation or treatment with a neutralizing antibody, supressed IL-33-induced chemotactic migration of microglia toward Aβ plaques. This finding suggests that VCAM1 has an essential role in driving Aβ-targeted microglial chemotaxis.

The researchers next conducted protein–protein interaction analysis of Aβ plaque-associated proteins to identify potential chemoattractants that interact with VCAM1. The analysis identified ApoE, along with three other proteins.

Stereotactic injection of beads coated with recombinant ApoE into APP/PS1 mice revealed an increase in microglia surrounding the beads when the mice were treated with IL-33. This increase was not observed with beads coated in the other VCAM1-interacting proteins, indicating that VCAM1–ApoE interaction directs IL-33-induced chemotactic migration of microglia.

Consistent with this hypothesis, inhibition of ApoE in the mice supressed migration of microglia towards Aβ plaques. Furthermore, subsequent induction of phagocytic microglia and clearance of Aβ was inhibited. These results provide evidence that interactions of $VCAM1^+$ chemotactic microglia with Aβ plaque-associated ApoE mediates the transition from chemotaxis to phagocytosis, in turn regulating Aβ clearance.

Last, the researchers confirmed that $VCAM1^+$ microglia interact with Aβ plaques in people with AD. Moreover, serum levels of soluble VCAM1 were higher in people with AD than healthy control individuals, and levels of VCAM1 in the cerebrospinal fluid inversely correlated with microglial infiltration into Aβ plaques.

"The increase in soluble VCAM1 in people with AD suggests that microglia surface receptors may be inhibited in age-related diseases, impairing microglial functions," concluded Ip. "The findings of this study suggest that targeting the VCAM1–ApoE signalling pathway could be a potential therapeutic strategy for AD."

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Related article: Lau, S. F. et al. IL-33-PU.1 transcriptome reprogramming drives functional state transition and clearance activity of microglia in Alzheimer's disease. *Cell Rep.* https://doi.org/10.1016/j.celrep.2020.107530 (2020)