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GENETICS

Single-cell transcriptomics analysis identifies oligodendrocyte-microglia crosstalk modulated by TREM2-R47H and exacerbated by APOE4 in Alzheimer's disease

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Abstract

Background: Alzheimer's Disease (AD) risk variants *APOE4* and *TREM2-R47H* are known to impact glial cell functions and transcriptional profiles. *TREM2*-mediated oligodendrocyte-microglial crosstalk has not been revealed in previous research studies. Here, we present novel findings suggesting a *TREM2*-dependent mediation of oligodendrocyte transcriptional profiles.

Methods: We investigated cell-type specific transcriptional changes associated with humanized *APOE4* and *TREM2-R47H* genotypes in P301S+ mice versus background controls via single-nuclei RNA-sequencing of the frontal cortex. We investigated cell type subcluster abundance in association with genotype, sex and tau-positivity. We classified subclusters through differentially expressed gene network modules and gene set enrichment analysis. We compared our findings in mice to a human cohort. The mouse cohort consisted of 52 humanized *APOExTREM2* mice, with six-to-eight mice per genotype-tau group, evenly split on sex. The human cohort consisted of 55 AD and control humans: *APOE4-carrier TREM2-R47H* (*E4-R47H*) (n = 18), *nonE4-R47H* (*nonE4-R47H*) (n = 6), *APOE4-carrier TREM2-common variant* (*E4-CV*) (n = 16), *nonE4-CV* (n = 6).

Results: We found that *APOE-TREM2* status had sex- and tau-independent *TREM2-R47H*-specific effects, and *APOE4-R47H* synergistic effects on cell abundance in oligodendrocytes, oligodendrocyte progenitor cells (OPCs), and a subgroup of inhibitory neurons. Specifically, we identified OPC and oligodendrocyte subclusters that strongly associate with *TREM2-R47H* in a tau-independent manner, further exacerbated by *APOE* genotype. Of note, the human cohort also showed a strong synergistic effect of *APOE4* and *TREM2-R47H* on an oligodendrocyte subcluster

that may be related to the *TREM2-R47H*-dependent oligodendrocyte subclusters identified in the mice. This finding of *TREM2*-specific effects on oligodendrocyte transcriptional states in both mice and humans suggests possible *TREM2*-mediated microglia-oligodendrocyte crosstalk, or the presence of *TREM2*-oligodendrocyte cell-ligand interactions that merits further investigation.

Conclusion: In summary, this study suggests possible synergistic effects of *APOE4*-carrier and *TREM2-R47H*-carrier status on OPC, oligodendrocyte, and inhibitory neuron abundance and transcriptional profiles. Specifically, OPCs and oligodendrocytes show a strong association with *TREM2-R47H* that is exacerbated by *APOE* genotype, a finding that is reflected in the human cohort. Hence, further classification of differences between joint *APOE-TREM2* genotypes will improve our understanding of glial cell alterations in AD, and could lead to novel cell type-specific therapeutic interventions for AD and other AD-related dementia if broadly applied.