Q&A: Uncovering how cellular miscommunication leads to cognitive impairment in female patients with Alzheimer's disease

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Lead author Neta Rosenzweig, Ph.D., of the Brigham and Women's Hospital Ann Romney Center for Neurological Diseases, and senior author Oleg Butovsky, Ph.D., of the Ann Romney Center and Gene Lay Institute of Immunology and Inflammation, share key messages from their paper titled "Sex-Dependent APOE4 Neutrophil-Microglia Interactions Drive Cognitive Impairment in Alzheimer's Disease" published in *Nature Medicine*.

How would you summarize your study for a lay audience?

In this manuscript, we identify that a major genetic risk factor for the late onset of Alzheimer's disease, APOE4, impairs the communication of immune cell neutrophils with immune cells of the brain microglia. This miscommunication leads to cognitive impairment in female Alzheimer's patients.

One of the mechanisms identified was related to the induced expression of an immune molecule called IL17F in neutrophils, which causes microglia not to respond to neurodegeneration. Our findings from blocking this molecule in preclinical models of Alzheimer's disease suggest a potential translational basis for unmet clinical needs.

What question were you investigating?

We asked how sex, APOE4, and cognitive status interact in regulating neutrophil phenotype and functions that impair microglial response to neurodegeneration.

We also asked whether APOE4 regulates neutrophils in a cell-autonomous manner and whether deleting APOE4 in neutrophils could affect microglial phenotype and AD pathology in mouse models.

What methods or approach did you use?

In collaboration with Reisa Sperling, MD, and Hyun-Sik Yang, MD, both of the Brigham's Department of Neurology, we isolated blood neutrophils from healthy controls (HC) and Alzheimer's disease (AD) donors expressing different APOE variants. In addition, in collaboration with Bart Eggen, Ph.D., of the University of Groningen, the Netherlands, we isolated microglia from the brains of HC and AD donors carrying different APOE variants as a guide to our original hypothesis, which was validated in humanized mouse models of AD.

Leveraging single-cell transcriptomics across APOE variants in both sexes, multiplex flow cytometry, and validation in two independent cohorts of APOE4 female AD patients, we identified a new subset of neutrophils interacting with microglia associated with cognitive impairment. We also used a humanized mouse model of AD designed to delete APOE variants only in neutrophils to validate our findings in human samples mechanistically.

What did you find?

We identified a new subset of neutrophils interacting with microglia associated with cognitive impairment. This phenotype is defined by increased IL-17 and IL-1 co-expressed gene modules in blood neutrophils and in microglia of cognitively impaired female APOE4 carriers, showing increased infiltration of the AD brain. APOE4 female IL-17^{+} neutrophils upregulated the immunosuppressive cytokines IL-10 and TGFb and immune checkpoints associated with accelerated immune aging, including LAG-3 and PD-1.

Deletion of APOE4 in neutrophils reduced this immunosuppressive phenotype and restored the microglial response to neurodegeneration

(MGnD), limiting plaque pathology in AD mice. Mechanistically, IL-17F upregulated in APOE4 neutrophils interacts with microglial IL-17RA to suppress the induction of MGnD phenotype, and blocking this axis supported cognitive improvement in AD mice.

What are the implications?

Our data indicate that targeting IL-17F may benefit APOE4 female carriers, who are less responsive to current anti-amyloid-beta therapeutics and develop amyloid-related imaging abnormalities as a common side effect of treatment with amyloid-lowering monoclonal antibodies. This may result in precise therapeutic interventions for AD according to sex and APOE4 genotype, providing an alternative strategy for an unmet clinical need.

What are the next steps?

The next steps include translating these findings into a potential therapeutic intervention for AD and continuing to investigate the immune landscape associated with cognitive impairment in patients to identify additional molecular targets.

More information: Neta Rosenzweig et al, Sex-dependent APOE4 neutrophil–microglia interactions drive cognitive impairment in Alzheimer's disease, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-03122-3

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