Illuminating the role of the adaptive immune response in neurodegeneration

Although neuroinflammation is thought to drive the pathology of age-related neurodegenerative diseases, little is known about the role of the adaptive immune response in Alzheimer's disease (AD). Researchers at Stanford University revealed immune repertoire and gene expression changes that occur in immune cells from the cerebrospinal fluid (CSF) in age-related neurodegeneration (AD and mild cognitive impairment (MCI)), including antigen-specific clonal expansion of $CD8^+$ T cells. D Gate et al., *Nature.* (2020).

Research questions	Snapshot
Are adaptive immune cells involved in age-related neurodegeneration? How does the immune repertoire change in patients with age-related neurodegeneration?	**Research area:** Neurodegenerative disease **Organism:** Human **Sample type:** Cerebrospinal fluid (CSF), Peripheral blood mononuclear cells (PBMCs) **10x Genomics product:** Chromium Single Cell Immune Profiling

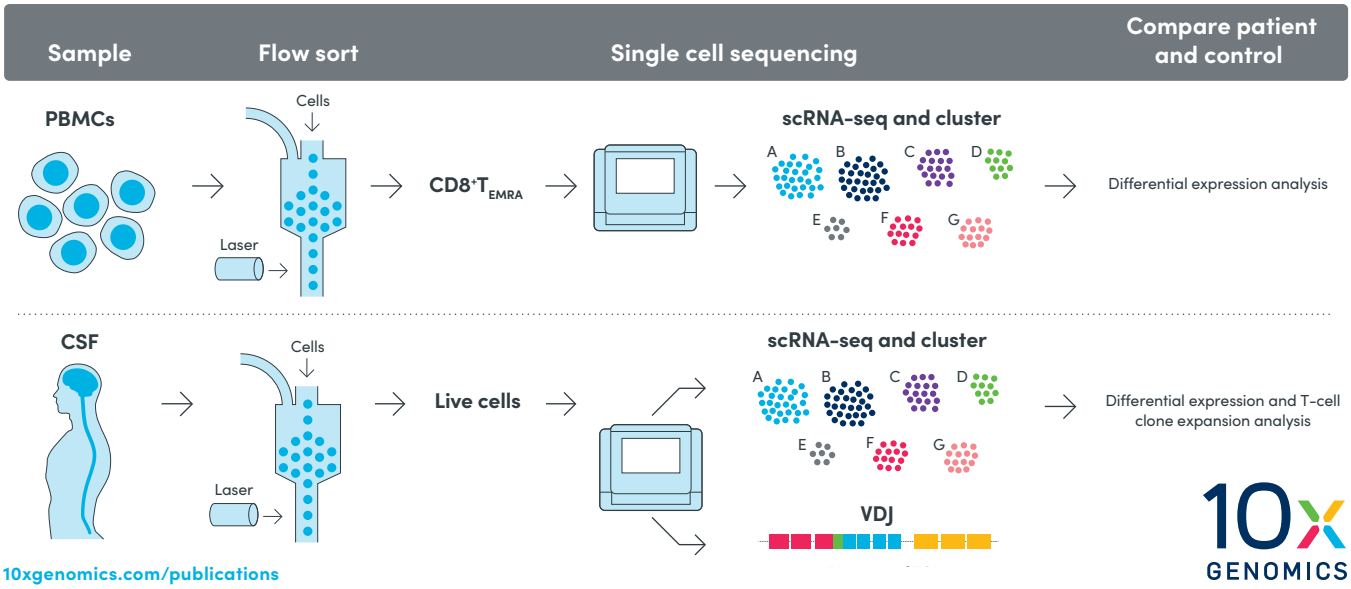
Experiment overview

Analysis of PBMCs

- Collected PBMCs from 7 healthy individuals and 6 individuals with AD or MCI
- Isolated peripheral $CD8^+$ T_{EMRA} cells using fluorescence-activated cell sorting (FACS)
- Compared mRNA expression in healthy versus AD or MCI individuals

Analysis of CSF

- Isolated live cells from the CSF using FACS from 9 healthy individuals and 9 individuals with AD or MCI
- Analyzed mRNA expression and full-length, paired T-cell receptor sequences for over 20,000 cells
- Compared expression in highly expanded TCR clones from AD or MCI samples to that of low-frequency clones



Why single cell?

The role of the adaptive immune system in neurodegenerative diseases, such as AD, is controversial. Fully understanding underlying disease mechanisms requires additional insights, including clarity into which T-cell clones are expanded in the disease state and the antigens to which they are responding. These questions can only be answered by analyzing gene expression and TCR sequences at single cell resolution.

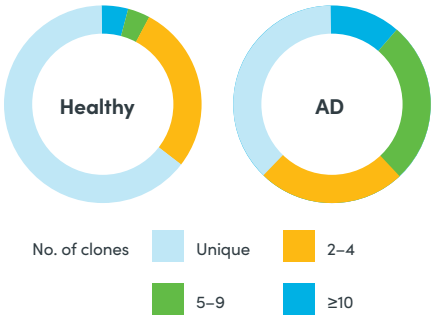


Figure 1. Adapted from Figure 3 of D Gate et al. Representative samples showing expanded clonality of T cells from CSF in patients with AD. Color coding denotes the proportion of the total TCRaß sequences represented by a given clone.

Computational analysis

The authors used the R package Seurat for filtering, variable gene selection, normalization, scaling, dimensionality reduction, clustering and visualization, and the MAST algorithm for differential expression analysis. After filtering and normalization, they performed a principal component analysis (PCA), using 10 principal components for clustering and a resolution of 0.4 t-SNE for visualization to analyze peripheral $CD8^+$ T_{EMRA} cells and 4 principal components and a resolution of 0.3 t-SNE to analyze CSF cells. They additionally used Panther for Reactome pathway analysis.

Results

After initial mass cytometry analysis identified an increase in peripheral $CD8^+$ T_{EMRA} cells in the blood of AD and MCI patients, the authors used single cell RNA sequencing (scRNA-seq) on isolated peripheral $CD8^+$ T_{EMRA} cells and found that these cells appeared to be more antigenically stimulated than cells from healthy patients.

To determine whether or not changes in the periphery are reflective of the immune response in the central nervous system, the researchers analyzed immune cells in the CSF using both whole transcriptome scRNA-seq and single cell identification of full-length, paired T-cell receptor sequences. They found that the CSF of AD and MCI patients had clonally expanded cytotoxic proinflammatory $CD8^+$ T_{EMRA} cells whereas healthy patients did not (Figure 1). Additional studies demonstrated that the clonal expansion is antigen-specific. These findings showcase an approach to investigate key immune changes in neurodegeneration and understand the impact of unique immune signatures in neurological disease.

References

1. D Gate et al., Clonally Expanded CD8 T Cells Patrol the Cerebrospinal Fluid in Alzheimer's Disease. *Nature.* 577, 399–404. (2020).

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