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Peripheral Immune Dysregulation in Parkinson's Disease: Integrative Analysis of Human Transcriptomics and Preclinical Validation

1.

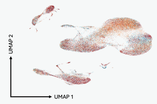
INTRODUCTION

- PARKINSON'S DISEASE (PD) IS A PROGRESSIVE NEURODEGENERATIVE DISORDER TRADITIONALLY CHARACTERIZED BY DOPAMINERGIC NEURON LOSS.
- THE DURA MATER HAS RECENTLY EMERGED AS A CRITICAL IMMUNOLOGICAL HUB AT THE CNS BORDER, WITH POORLY UNDERSTOOD ROLES IN NEURODEGENERATIVE DISEASE.
- EMERGING EVIDENCE IMPLICATES PERIPHERAL IMMUNE DYSREGULATION AS A POTENTIAL CONTRIBUTOR TO DISEASE PATHOGENESIS.
- UNDERSTANDING HOW CIRCULATING IMMUNE CELLS ARE ALTERED IN PD MAY REVEAL EARLY BIOMARKERS OR THERAPEUTIC TARGETS

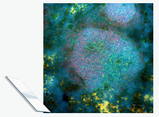
OBJECTIVE

- Characterize peripheral immune cell alterations in PD using single-cell transcriptomic data.
- Validate key immune signatures in a preclinical PD mouse model using immunofluorescence.

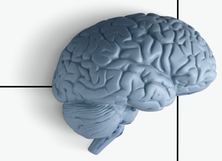
Publicly available PBMC transcriptomic datasets from PD patients and healthy controls → Clustering, differential expression, and pathway analysis



Identification of altered lymphocyte populations and immune gene expression patterns (e.g., CD8⁺ T cell activation)



α-Synuclein injected PD mouse model → Flow cytometry and immunofluorescence of dura, spleen, and gut



2.

FIGURE 1. TRANSCRIPTOMIC PROFILING OF PBMCS REVEALS ALTERED LYMPHOCYTE STATES IN PARKINSON'S DISEASE

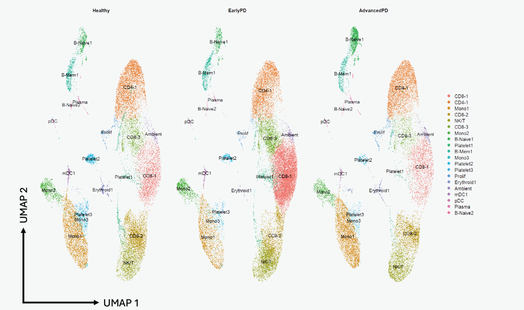


Figure 1A. UMAP of PBMC Clusters by Disease Stage. Transcriptomic profiling of PBMCs reveals altered lymphocyte states in Parkinson's Disease.

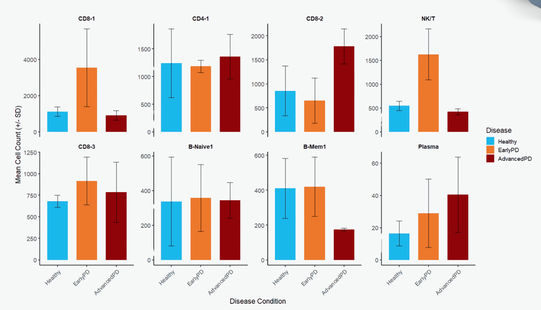
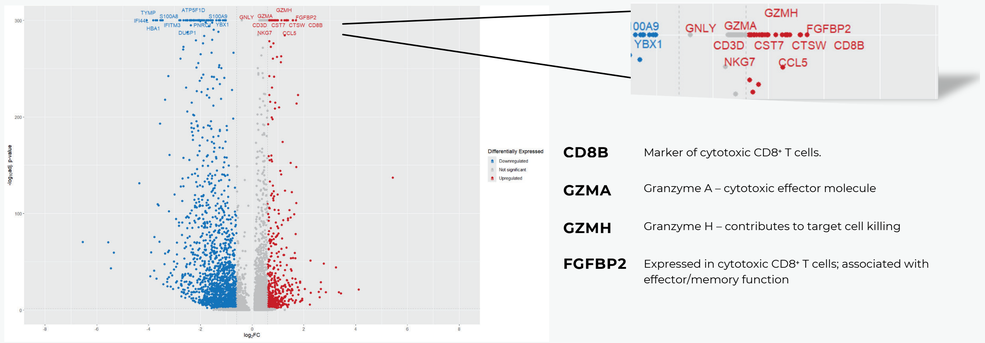


Figure 1B. Lymphoid Cell Cluster Abundance Across Disease States. Transcriptomic profiling of PBMCs reveals altered lymphocyte states in Parkinson's Disease.



CD8B	Marker of cytotoxic CD8⁺ T cells.
GZMA	Granzyme A – cytotoxic effector molecule
GZMH	Granzyme H – contributes to target cell killing
FGFBP2	Expressed in cytotoxic CD8⁺ T cells; associated with effector/memory function

Figure 1C. Volcano plot showing differentially expressed genes between healthy and PD groups. Notable upregulated genes include **CD8B**, **GZMA**, **GZMH**, and **FGFBP2**, consistent with expansion and activation of cytotoxic CD8⁺ T cells in PD. FGFBP2 is a marker of highly cytotoxic, proliferative CD8 T cells and has been implicated in neuroinflammatory states. (Xiong et al., 2024)

3.

MOUSE FLOW CYTOMETRY: T CELLS IN DURA

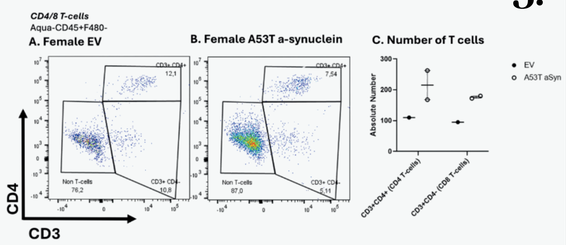


Figure 2. Flow cytometric identification of CD3⁺CD4⁺ and CD3⁺CD8⁺ T cells in the dura mater of α-synuclein-injected mice.

4.

IMMUNOFLUORESCENCE ANALYSIS OF SPLEEN TISSUE REVEALS COMPARTMENT-SPECIFIC IMMUNE CHANGES IN PD.

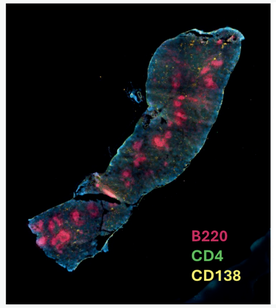


Figure 3a. Spleen 10x EV.

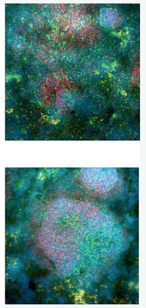


Figure 3b. Spleen 20x EV vs α-Syn

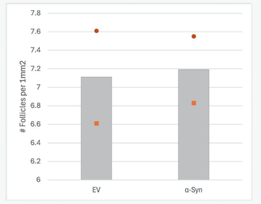


Figure 3c. Number of spleen follicles per1mm2. Squares depict females and circles depict males.

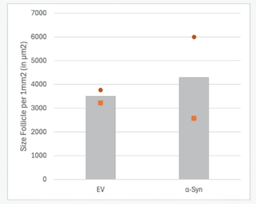


Figure 3d. Size of spleen follicles per1mm2, represented in µm2. Squares depict females and circles depict males.

5.

PD MICE SHOW IMMUNE SHIFTS IN SMALL AND LARGE INTESTINE

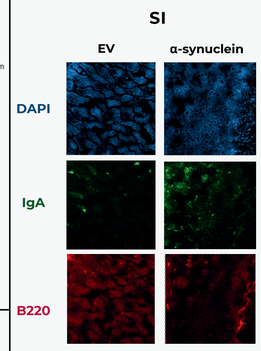


Figure 4a. Representative immunofluorescence images of IgA and B cells in small intestine of EV and α-Synuclein mice.

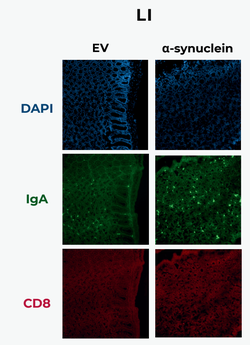


Figure 4b. Representative immunofluorescence images of IgA and CD8 T cells in large intestine of EV and α-Synuclein mice.

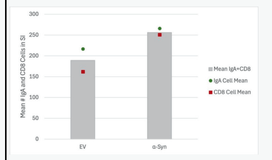


Figure 4c. Mean number of IgA and CD8 cells in EV and α-Synuclein groups of both sexes insmall intestine. Mean IgA cells are depicted in green circles and mean CD8 cells are depictedin red squares.

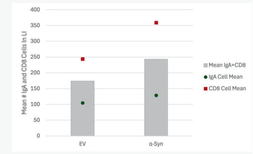


Figure 4d. Mean number of IgA and CD8 cells in EV and α-Synuclein groups of both sexes inlarge intestine. Mean IgA cells are depicted in green circles and mean CD8 cells are depictedin red squares.

KEY FINDINGS

FINDING 1.

Transcriptomic analysis of PBMCs revealed immune alterations in PD patients, with changes in CD8⁺ T cells and B cell subsets.

FINDING 2.

In a preclinical mouse model, CD8⁺ T cells were increased in the dura, with additional immune cell shifts observed in the spleen, small intestine, and large intestine.

FINDING 3.

Immunofluorescence quantification demonstrated disrupted lymphoid architecture and altered immune cell distribution, with preliminary evidence of sex-dependent differences.

FUTURE DIRECTIONS

- Validate murine findings in **human peripheral organs** (spleen, gut, dura) to establish translational relevance.
- Expand sample size in both human and preclinical cohorts to rigorously **assess sex-specific immune alterations.**
- Functionally characterize CD8⁺ T cell subsets, with focus on the **IL-7Rα^low effector phenotype**.
- Use **gain- and loss-of-function** approaches in PD models to determine contributions of **CD8⁺ T cells and B cells** to disease progression.
- Investigate immune dysregulation in the **meningeal niche** to clarify how **dura immunity** impacts neurodegeneration.

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