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Immune Network Dysregulation of the Central Nervous System in Parkinson's Disease

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Parkinson's disease (PD), the second most common neurodegenerative disorder affecting about 1% of individuals over 60, is marked by progressive dopaminergic neuron loss and α-synuclein aggregation. Rapid eye movement (REM) sleep behavior disorder (RBD), a parasomnia characterized by dream enactment and the loss of skeletal muscle atonia during REM sleep, is a prodromal α-synucleinopathy and often precedes the clinical onset of PD. While neuroinflammation has been implicated in PD pathogenesis, the specific molecular and cellular mechanisms linking early immune activation to neurodegeneration remain poorly defined.

To investigate neuroimmune interactions in PD, we combined single cell genomics, proteomics, neuroimmunology, and microbiome analyses across multiple anatomical compartments, brain, cerebrospinal fluid (CSF), blood, and gut from individuals at various disease stages. We conducted single nucleus transcriptomic and proteomic profiling of the prefrontal cortex in postmortem brain tissue from individuals with late-stage PD and matched controls. This revealed distinct transcriptional changes across eight major brain cell types, including elevated brain-resident T cells and abatement of neuron-astrocyte interactions. Lewy body pathology correlated inversely with molecular chaperone expression in excitatory neurons, while synaptic proteins were broadly downregulated, pointing to neuron-specific vulnerability and disrupted cell-cell communication. Comparison with Alzheimer's disease datasets highlighted shared glial signatures but divergent neuronal responses, supporting disease-specific neurodegenerative mechanisms.

In an ongoing clinical study, we profiled over 1 million immune cells from paired CSF and blood samples of 84 individuals, including 34 with RBD, 18 with PD without RBD, 15 with PD and RBD, and 15 age-matched healthy controls generating the first human single-cell CSF atlas of RBD and PD. Surprisingly, we identified a pleocytosis in the CSF, most pronounced in patients with RBD, similar to what is observed in patients with early autoimmune multiple sclerosis (MS). In marked contrast to MS, with single cell RNA sequencing, we revealed increases in CSF-specific microglia-like macrophages expressing JAK-STAT and TNFα signaling signatures in prodromal PD, with a lack of T cell activation in the CSF. These human CSF macrophages exhibited similar transcriptional profiles to dural macrophages from human α-synuclein-expressing PD model mice. These findings uncover a myeloid-mediated TNFα inflammatory process in the CNS of patients with prodromal PD, suggesting a novel pathological mechanism in disease etiology.

Together, these integrative findings support a model of PD pathogenesis driven by immune dysregulation in the central nervous system involving adaptive immunity and innate myeloid

neuroinflammatory responses. This work provides a foundation for mechanistically guided therapeutic strategies targeting early immune processes in both prodromal and established PD.