

In Vivo Profiling of Cell Type–Specific Proteomic Responses to Tau Pathology

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Introduction

Tauopathies are a heterogeneous group of neurodegenerative diseases characterized by the accumulation of hyperphosphorylated tau into insoluble aggregates in the brain. Tau pathology is associated with neuronal loss, inflammation, and reactive gliosis; however, cell type-specific proteomic responses to tau accumulation across different brain cell populations remain poorly understood. To address this knowledge gap, we performed cell type-specific proteomic profiling in a mouse model of tauopathy.

Methods

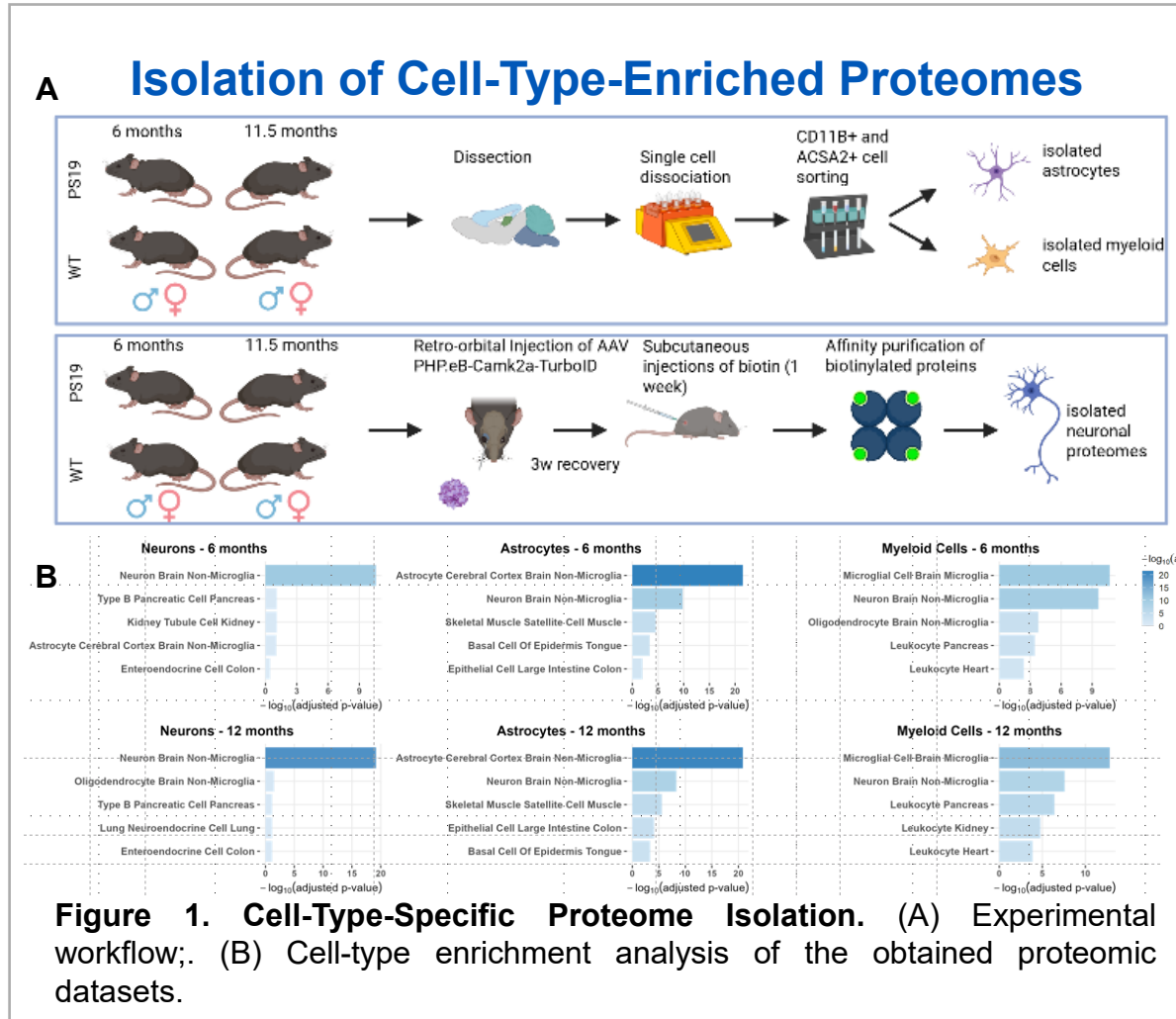
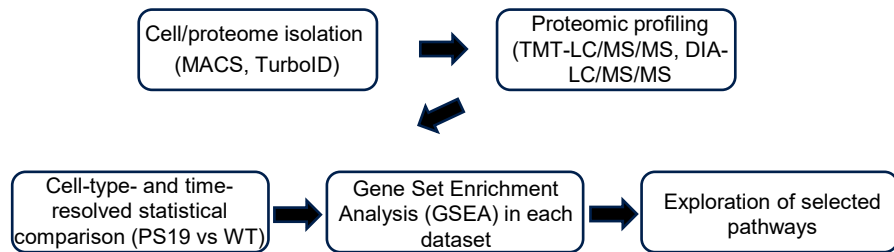


Figure 1. Cell-Type-Specific Proteome Isolation. (A) Experimental workflow;. (B) Cell-type enrichment analysis of the obtained proteomic datasets.

Proteomic Changes in Astrocytes Precede Myeloid Cell Activation

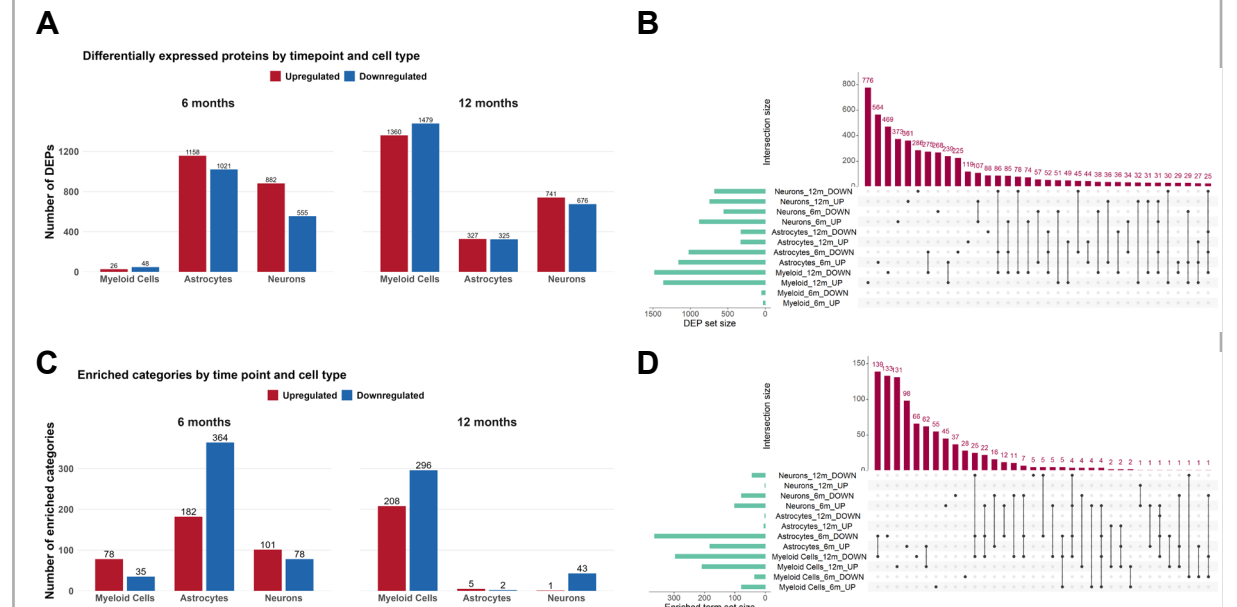


Figure 2. Proteomics Results Overview. (A) Number of differentially abundant proteins (DAPs) at each cell type and time point. (B) Overlap among cell type- and time point-specific DAPs. (C) Number of significantly enriched terms and pathways identified by Gene Set Enrichment Analysis (GSEA). (D) Overlap among cell type- and time point-specific GSEA-enriched terms and pathways

Early Astrocytic Proteomic Changes in RNA Processing

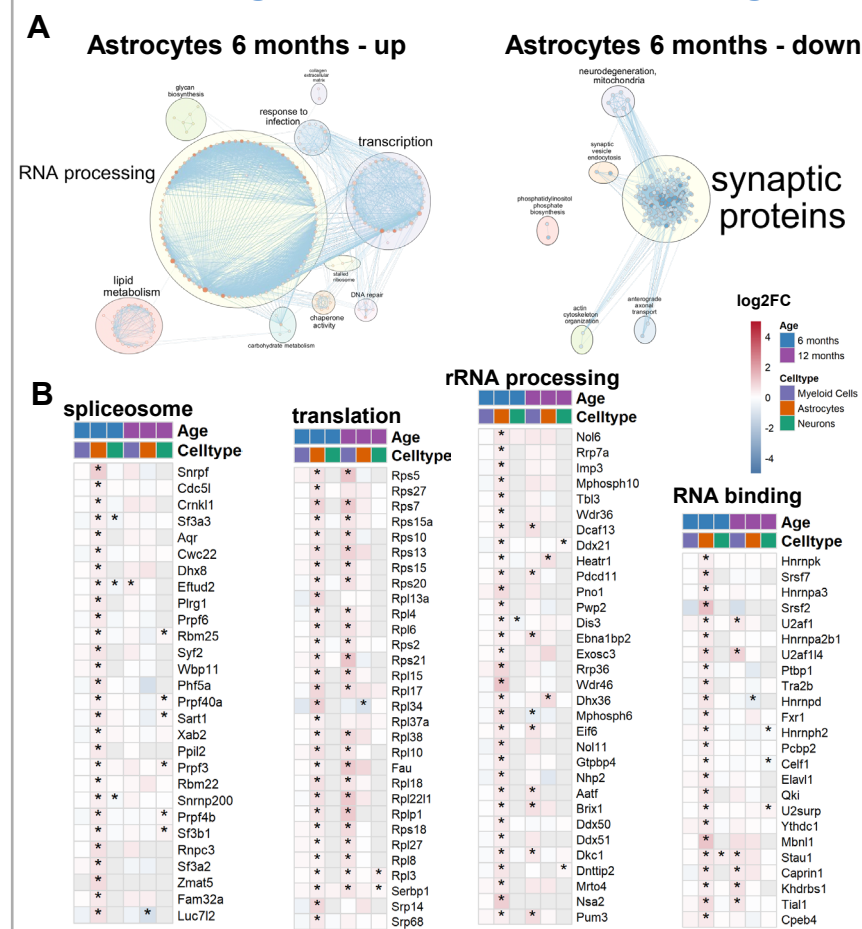


Figure 3. Upregulation of RNA Processing and Translation Proteins in PS19 Astrocytes. (A) Clustered annotated enrichment maps for up- and downregulated pathways in PS19 astrocytes at 6 months (B) Clustered heatmaps showing fold changes of selected increased PPI protein modules. * - FDR < 0.05
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Interferon Signaling Activation in Glia

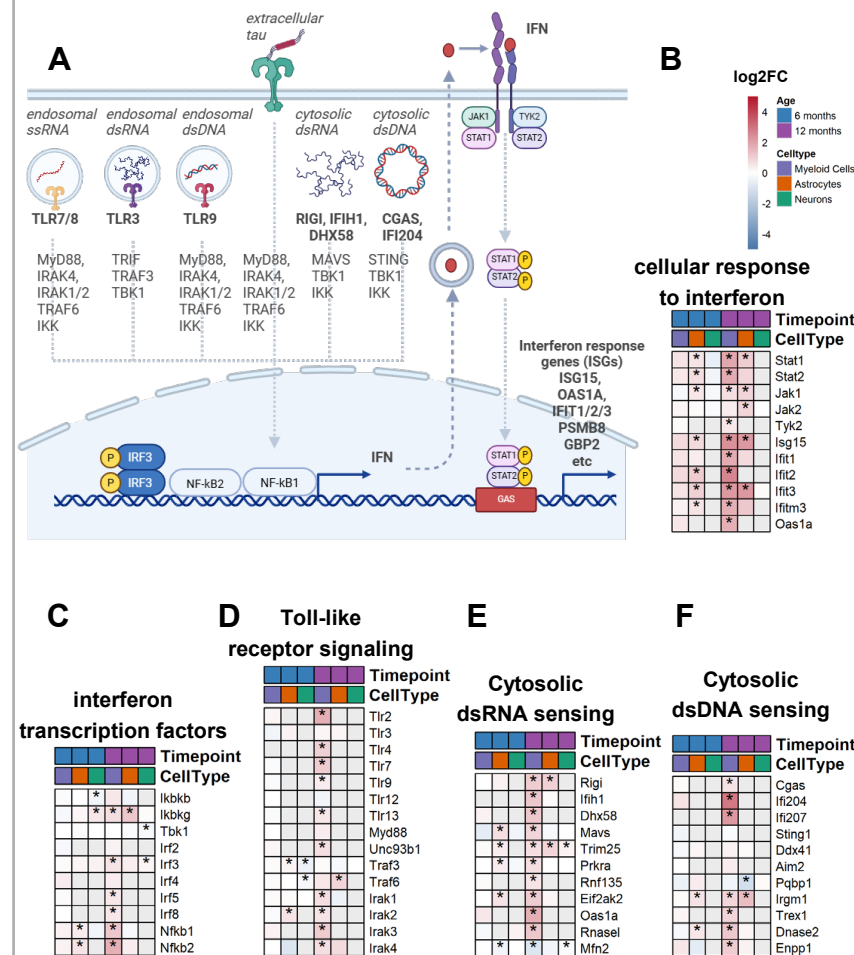


Figure 4. Interferon Signaling Activation in PS19 Mice. (A) Scheme of interferon signaling (B-G) Clustered heatmaps showing fold changes of selected protein signatures for pathways upstream and downstream of interferon production. * - FDR < 0.05

Cell Type-Specific Energy Metabolism Changes in Neurons and Astrocytes

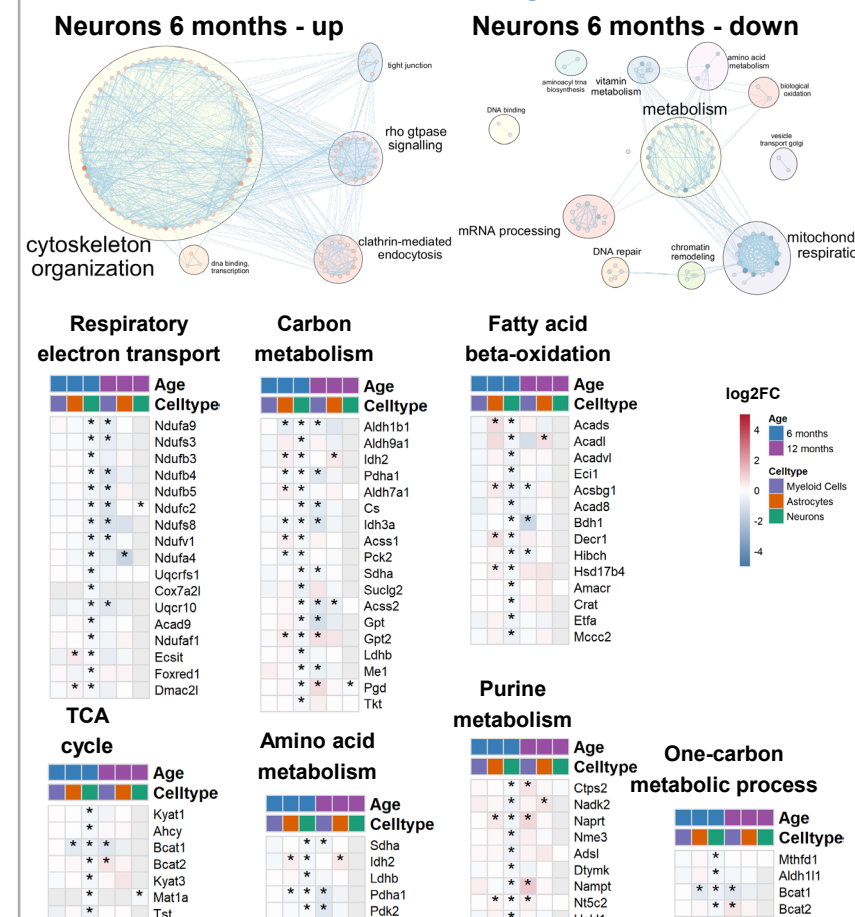


Figure 5. Changes in Neuronal Metabolic Proteome in PS19 Mice (A) Clustered annotated enrichment maps for up- and downregulated pathways in PS19 neurons at 6 months. (B) Clustered heatmaps showing fold changes of selected decreased PPI protein modules. * - FDR < 0.05

Conclusions

- Cell-type-specific proteomics identified a time- and cell-type-dependent response to tau pathology in PS19 mice.
- At 6 months, astrocytes show stronger proteomic response to tau pathology in PS19 mice than microglia/myeloid cells
- Early astrocytic response to tau pathology in PS19 mice associated changes in proteins linked to transcription and translation
- Glial proteomes show evidence of interferon-related pathway activation
- Tau pathology in PS19 mice is associated with early metabolic remodeling in neurons and astrocytes

Acknowledgements

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