Spatial-Temporal Gene Expression Analysis of a Transgenic Model of Tauopathy in Alzheimer's Disease

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Introduction

- **Alzheimer's disease (AD) is a neurodegenerative disorder that leads to the progressive decline of memory, speech, visuospatial processing, and general cognitive capacity.**
- **An estimated 50 million people suffer from AD worldwide, a number that is expected to triple by 2050.**
- **AD is classically identified by amyloid-β plaque deposition in the hippocampal and cortical regions of the brain.**
- **A second pathological hallmark of AD is the aggregation of intracellular p-tau (tau), which leads to the formation of neurofibrillary tangles.**
- **Cuello's laboratory has previously developed a transgenic rat lineage of tauopathy, which models the pathophysiological and behavioral features of AD.**
- **This project aimed to investigate gene expression changes in tau compared to WT animals by identifying gene markers of early and late AD using spatial transcriptomics.**

Methods

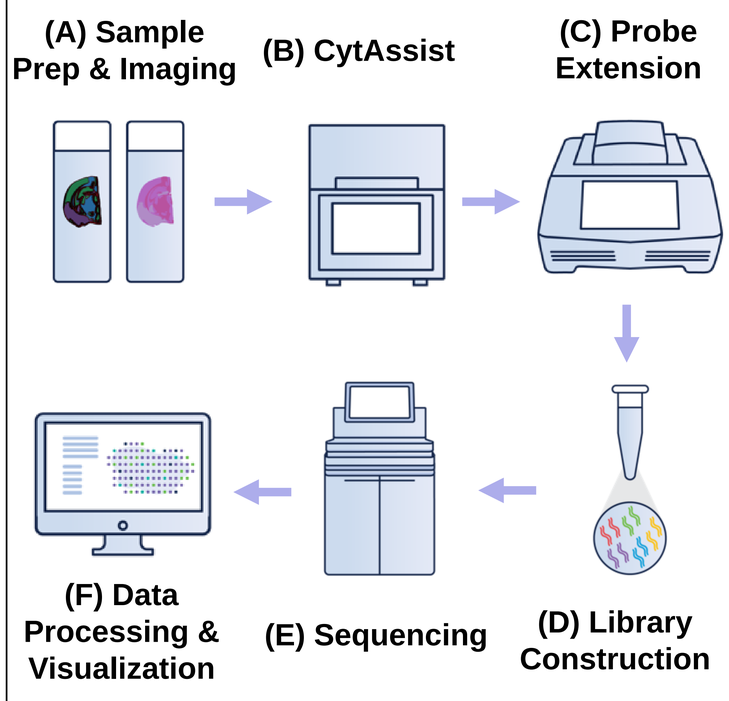

***Fig.1*: Workflow of Visium spatial transcriptomics. (A)** Coronal cryosections of young (10-months-old tau model and wild type) and aged (20-months-old tau model and wild type) rat brains were stained with H&E on standard glass slides. Sections at bregma level -3.6 mm were selected for analysis after microscopic inspection. **(B)** Within the CytAssist instrument, a brightfield image is captured to provide spatial orientation for data analysis, followed by hybridization of transcriptomic probes to a Visium slide. **(C/D/E)** A reverse transcription reaction produces barcoded cDNA from the previously captured mRNA. The barcoded cDNA is then pooled for downstream processing to generate a sequencing-ready library. **(F)** Space Ranger analysis software is then used to process the sequencing data, before being analyzed with the R package Seurat.

UMAP Cell Clustering

***Fig.2*: UMAP cell clustering and mapping of brain regions. (A)** UMAP plot illustrates clustering of cell-specific markers that was labelled corresponding to anatomical area via a reference database. Each color represents a brain region. **(B/C)** The clustering data was then mapped to the histological tissue samples, where individual anatomical areas are also defined by a single color.

TRIL Expression in the DG

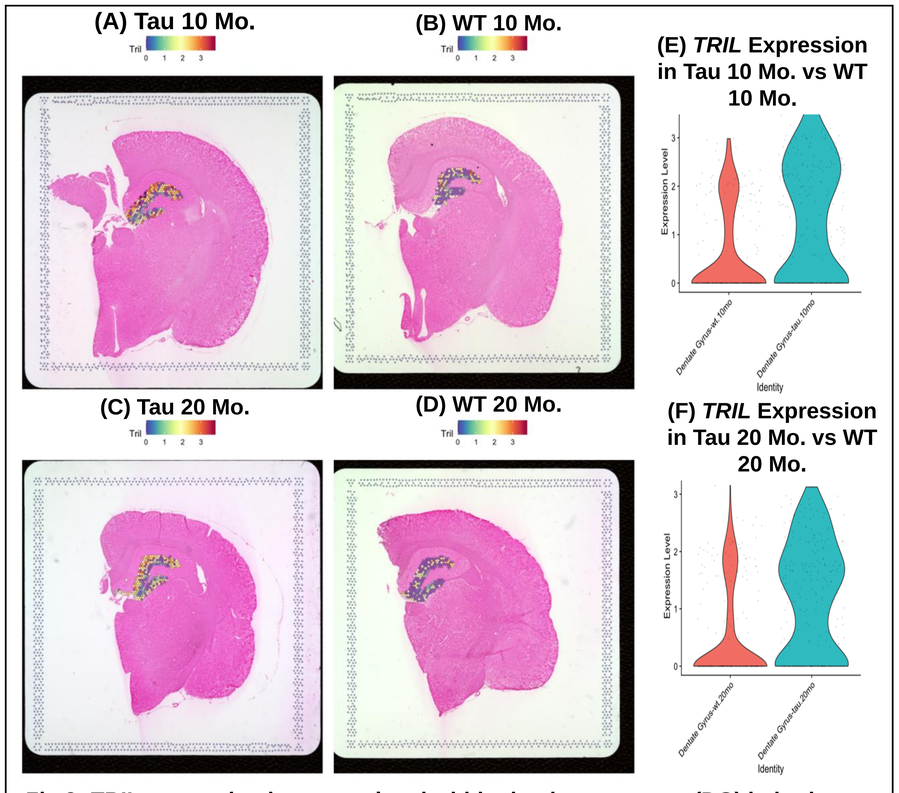

***Fig.3*: *TRIL* expression is up-regulated within the dentate gyrus (DG) in both young and old AD model.** Tissue images show the level of expression of *TRIL* within the dentate gyrus of 10-months-old tau **(A)** and wild type **(B)** models, and 20-months-old tau **(C)** and wild type **(D)** models. Violin plots illustrate the differing levels of expression of TRIL in 10-months-old wild type vs tau models **(E)**, and 20-months-old wild type vs tau models **(F)** .

Molecular Pathway Analysis

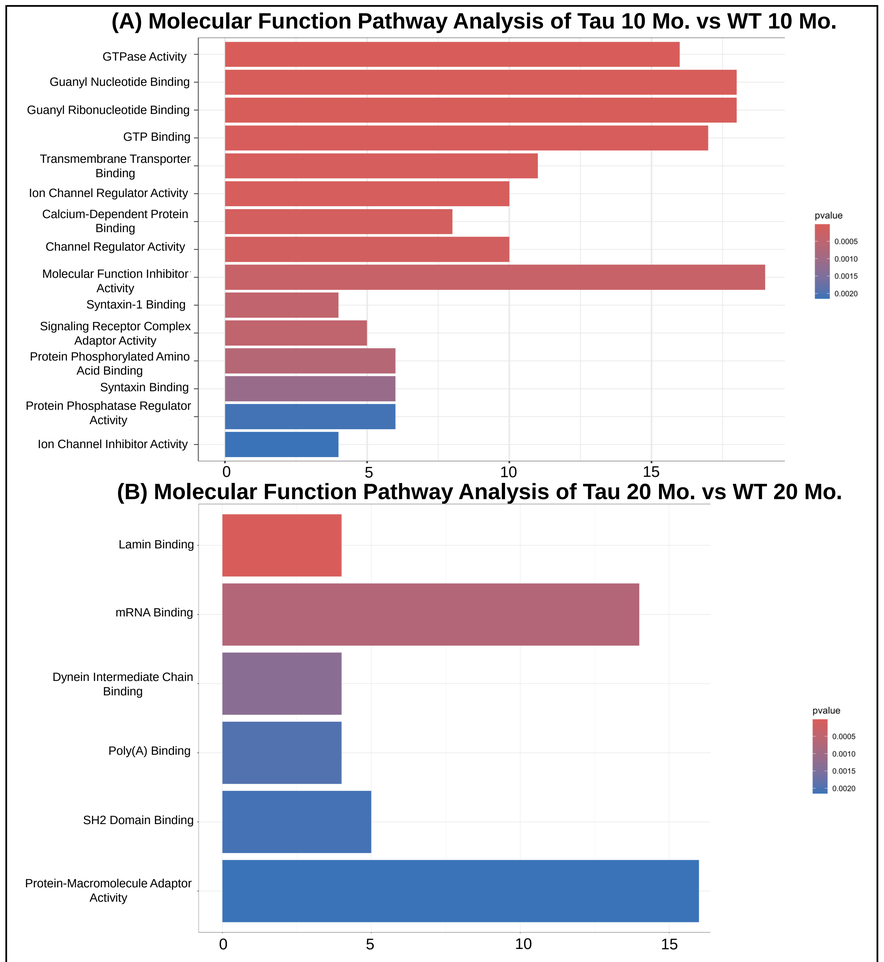

***Fig.4*: Molecular function pathway analysis reveals distinct gene-specific pathways between aging and young AD models**. Gene Ontology analysis comparison of differentially expressed genes in 10-month-old tau versus wild type **(A)** and 20-month-old tau versus wild type **(B)**, with color indicating the magnitude of the p-value.

Results & Conclusion

- **In the dentate gyrus of both early and late AD, *TRIL*, a gene linked to the progression of neurofibrillary tangles, was significantly up-regulated.**
- **Pathway analysis in the early AD model revealed significant changes in gene expression related to synaptic function, particularly in GTPase activity and ion-channel function.**
- **The late-stage model exhibited significant changes in gene expression associated with mRNA binding and dynein transport.**
- **These results indicate that spatial-temporal variations in gene expression at different stages of AD may include distinct molecular pathways and regional protein expression reflective of AD development.**

References

- Emmerson JT, Do Carmo S, Liu Y, Shalhoub A, Liu A, Bonomo Q, Malcolm JC, Breuillaud L, Cuello AC. Progressive human-like tauopathy with downstream neurodegeneration and neurovascular compromise in a transgenic rat model. Neurobiol Dis. 2023 Aug;184:106227. doi: 10.1016/j.nbd.2023.106227. Epub 2023 Jul 16. Erratum in: Neurobiol Dis. 2023 Oct 15;187:106301. doi: 10.1016/j.nbd.2023.106301. PMID: 37454780.
- Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. Lancet. 2021 Apr 24;397(10284):1577-1590. doi: 10.1016/S0140-6736(20)32205-4. Epub 2021 Mar 2. PMID: 33667416; PMCID: PMC8354300.