AGBT 2026, #433

Mapping organelle-associated mRNA localization in Alzheimer's disease brain via spatial multiomics

Ashley Heck[1], Kimberly Young[1], Rachel Liu[1], Joe Phan[1], Margaret Hoang[1], Lidan Wu[1], Aster Wardhani[1], Claire Williams[1], Sayani Bhattacharjee[1], Courtney Anderson[1], Prajan Divakar[1], Mirko Corselli[1], Joseph Beechem[1]

[1]Bruker Spatial Biology, Seattle WA 98109

Introduction

High-plex spatial profiling of brain tissue is challenged by the morphological complexity of neurons, whose extended processes rely on precise subcellular organization to support signaling and plasticity. Localized RNA translation and organelle positioning- particularly mitochondrial enrichment at synapses- are critical for neural function and are disrupted in neurodegenerative diseases such as Alzheimer's disease (AD). However, most spatial omics workflows focus on the soma, leaving much of this biology unprofiled. Here, we use the CosMx® Spatial Molecular Imager (SMI) to enable high-plex, same-section protein and RNA detection, allowing improved segmentation of neural projections and subcellular compartments to study cell- and organelle-resolved alterations in AD brain tissue. This work introduces tools to study mitochondrial spatial biology in AD as well as cancer, where neurons transfer mitochondria to cancer cells to support tumor metabolism (Ref 1).

Multiomic workflow overview

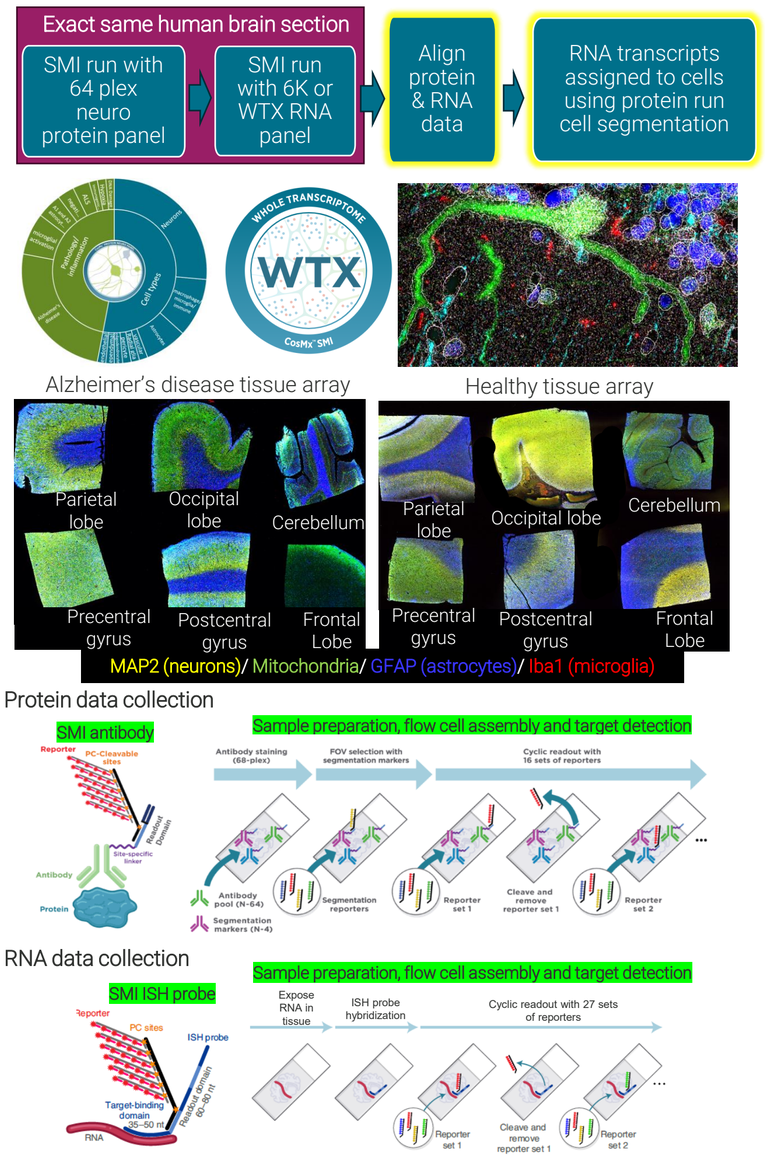


Fig 1. The SMI multiomics assay sequentially detects protein and RNA targets with oligonucleotide barcode-conjugated antibodies and barcoded RNA probes via several rounds of reporter binding and fluorescence imaging. Cells are segmented based on protein stains and decoded RNA targets are assigned to individual cells.

Protein augments segmentation and detection of transcripts and organelles

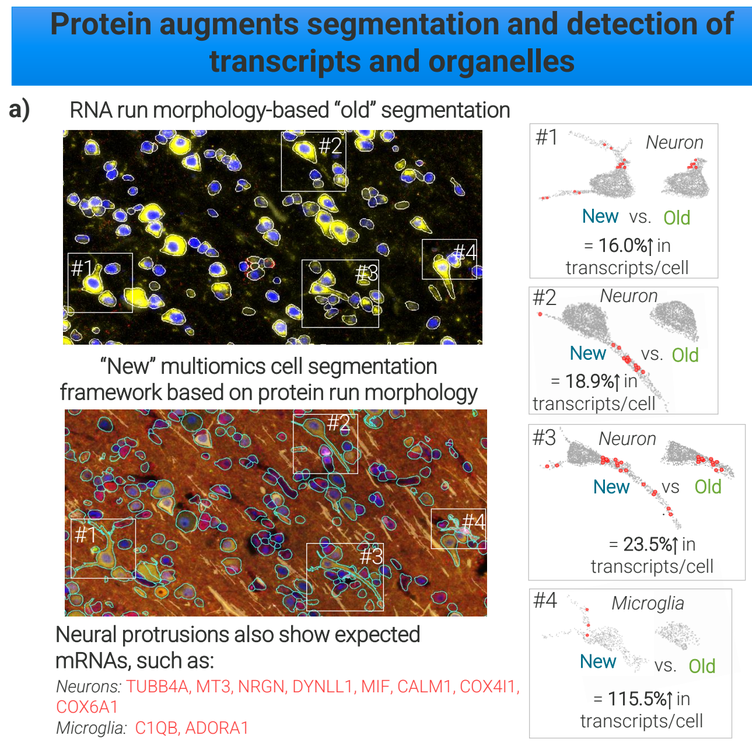


Fig 2. Multiomics segmentation captures neuronal and glial processes, mitochondria, and their transcripts. Protein- vs. RNA-based segmentation improves transcripts per cell (a), with examples capturing 6K transcripts (b) and mitochondria (c). Mitochondria-associated mRNAs colocalize with mitochondrial signal, supporting spatial mitochondrial biology insights (d). NDUFA10/NDUFA3: respiratory chain subunits; ATP5F1B/ATP5F1A: ATP synthase; MRPS28: ribosome component; DNAJA3: Hsp40 co-chaperone; SDHA: succinate dehydrogenase subunit- all associated with mitochondria.

Integrated RNA and protein signatures for confident cell type identification

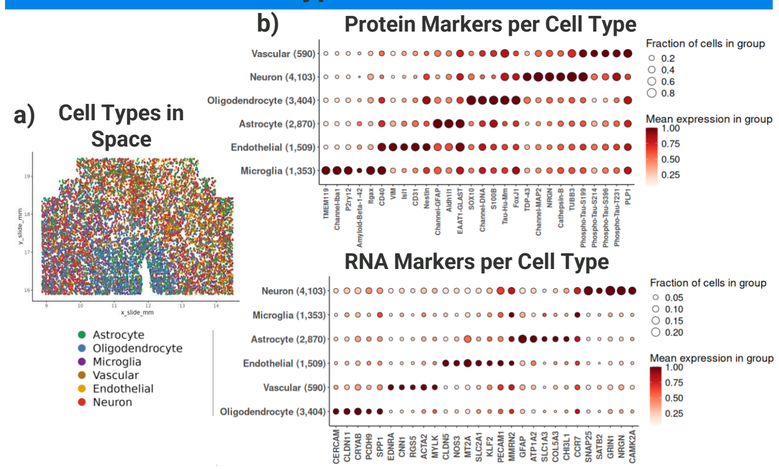
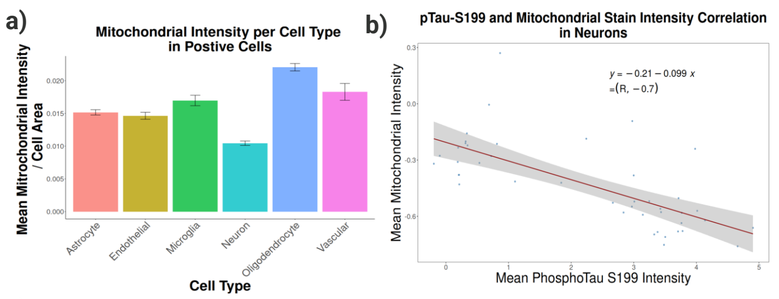


Fig 3. Example major cell types derived from multiomic marker-based algorithm "HieraType". (a) Spatial distribution of cell types in the AD parietal lobe shows expected patterns (neurons in gray matter). (b) Protein and RNA markers show canonical expression in expected cell types (e.g. MAP2 protein and SNAP25 RNA in neurons).

Mitochondrial signal differs across brain cell types and changes with proximity to AD pathology



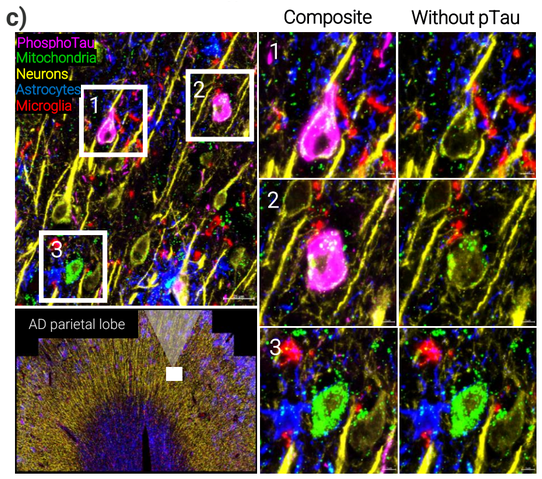


Fig. 4. (a) Mitochondrial intensity per area differs across AD parietal lobe cell types. (b) Neurons with high phospho-Tau S199 show reduced mitochondrial intensity. (c) Representative images highlight mitochondrial loss in phospho-Tau–positive neurons, consistent with AD-associated mitochondrial dysfunction (Ref 2).

Conclusions

Using SMI, we achieve 64-plex protein and WTX RNA detection that:

- Captures neural projections and associated transcripts and organelles
- Improves cell typing by integrating protein and RNA signatures
- Reveals mitochondrial changes in neurons associated with AD pathology
- Showcases the capability of SMI to profile spatial mitochondrial biology with important implications for understanding AD as well as cancer pathology (Ref 1)

References

1. Hoover G, et al. Nerve-to-cancer transfer of mitochondria during cancer metastasis. *Nature*. 2025;644:252–262
2. Reiss AB, et al. Mitochondria in Alzheimer's disease pathogenesis. *Life*. 2024;14(2):196.

Scan here to download or learn more