Deciphering the single Neuronal Death Narrative: Sub-Micron Spatial Omics via water Cluster/C60 /Plasma SIMS

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Abstract Content:

Mapping the precise molecular cascades in individual cells that govern neuronal death is critical to uncovering the mechanisms and progression of neurodegeneration. However, mapping these intricate biochemical shifts has long been hindered by the trade-off between spatial resolution and single-cell molecular identification. Furthermore, the critical need to preserve pristine chemical gradients is frequently unmet, as these transient signals are typically lost during conventional sample preparation without a dedicated cryogenic workflow.

We present an advanced secondary ion mass spectrometry (SIMS) approach engineered to decode the spatial omic narrative of single deteriorating neurons. By leveraging multiple primary ion beams—specifically water cluster $(H_2O)_n{}^+{}_{n\geq 28,000}$, $C_{60}{}^+$, and focused Xe^+ plasma beam—in tandem with a specialized cryogenic workflow to preserve volatile and transient biomolecules, unprecedented micron to sub-micron lateral resolution was achieved. This configuration enhances molecular ion detection of metabolites, lipids, and peptides in cells/tissues while simultaneously accommodating antibody-based cell-identity detection in a single sample. To process these multi-modal datasets, algorithms were developed to

segment single cells, co-register cell death hallmarks to identified cells, and perform advanced spatial clustering analysis. The detection of low-abundance cell-death hallmarks was validated via Cryo-3D imaging of single HT22 cells, a mouse hippocampal neuronal line.

The workflow allowed for the simultaneous interrogation of endogenous omics profiles across different cell types without losing spatial context in tissues affected by traumatic brain injury (TBI). The co-optimized analytical and computational workflow successfully mapped localized biochemical transitions and resolved cellular boundaries. The downstream segmentation and clustering algorithms accurately isolated single-cell data, linking specific metabolic and lipidomic shifts to phenotypic hallmarks of ferroptotic death.

These findings demonstrate that high-resolution cluster/plasma SIMS successfully bridges the gap between ultrastructural imaging and untargeted spatial metabolomics. By capturing the final molecular signatures of individual neurons and mapping cellular crosstalk during neural decay, this methodology offers a rare opportunity to dissect neurodegenerative pathways and evaluate targeted neuroprotective therapeutics.

Reference：

Key words： Cryo-SIMS, Sub-micron Spatial Omics, Single-Cell Analysis, and Ferroptosis