DOI: 10.1002/alz70855_100247

BASIC SCIENCE AND PATHOGENESIS

PODIUM PRESENTATION

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

MOLECULAR AND CELL BIOLOGY

Vulnerability of the Myelin-Axon Interface Uncovered by Subcellular Proteomics and Imaging of Alzheimer's Human Brain

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Abstract

Background: Myelin ensheathment is essential for rapid axonal electrical conduction, metabolic support and neuronal plasticity. In Alzheimer's disease (AD), disruptions in both myelin and axonal structures occur; however, the underlying mechanisms remain poorly understood.

Method: To investigate the molecular and cellular mechanisms of myelin-axon disruption, we developed novel proximity labeling subcellular proteomics of the myelin-axon interface in postmortem human brains and AD-model mice. We developed new computational algorithm to uncover cell-cell-communication between myelin-axon and their disruption in AD humans. We applied super-resolution expansion microscopy and high-resolution confocal imaging to AD human postmortem brains and AD-model mice to reveal myelin-axon disruption and pathological changes.

Result: Using proximity labeling subcellular proteomics of the myelin-axon interface in postmortem human brains and AD-model mice, we discovered dysregulated signaling pathways and ligand-receptor interactions, including those involved in β-amyloid processing, axonal outgrowth and lipid metabolism. Expansion microscopy confirmed the subcellular expression of top proteomic hits and revealed β-amyloid aggregation within internodal peri-axonal space and paranodal/juxtaparanodal channels. Although no overt changes in myelin coverage were observed, we found reduced paranode density and aberrant myelination and paranode positioning around amyloid plaque-associated dystrophic axons.

Conclusion: These findings highlight the myelin-axon interface as a critical site of protein aggregation and disrupted neuro-glial communication in AD. The molecular architecture of the myelin-axon interface uncovered in this study provides a foundation for future mechanistic investigations in health and disease.