

RNA-Dependent Neuroimmune Condensates Link Complement C1q To Amyloid Pathology In Alzheimer’s Disease

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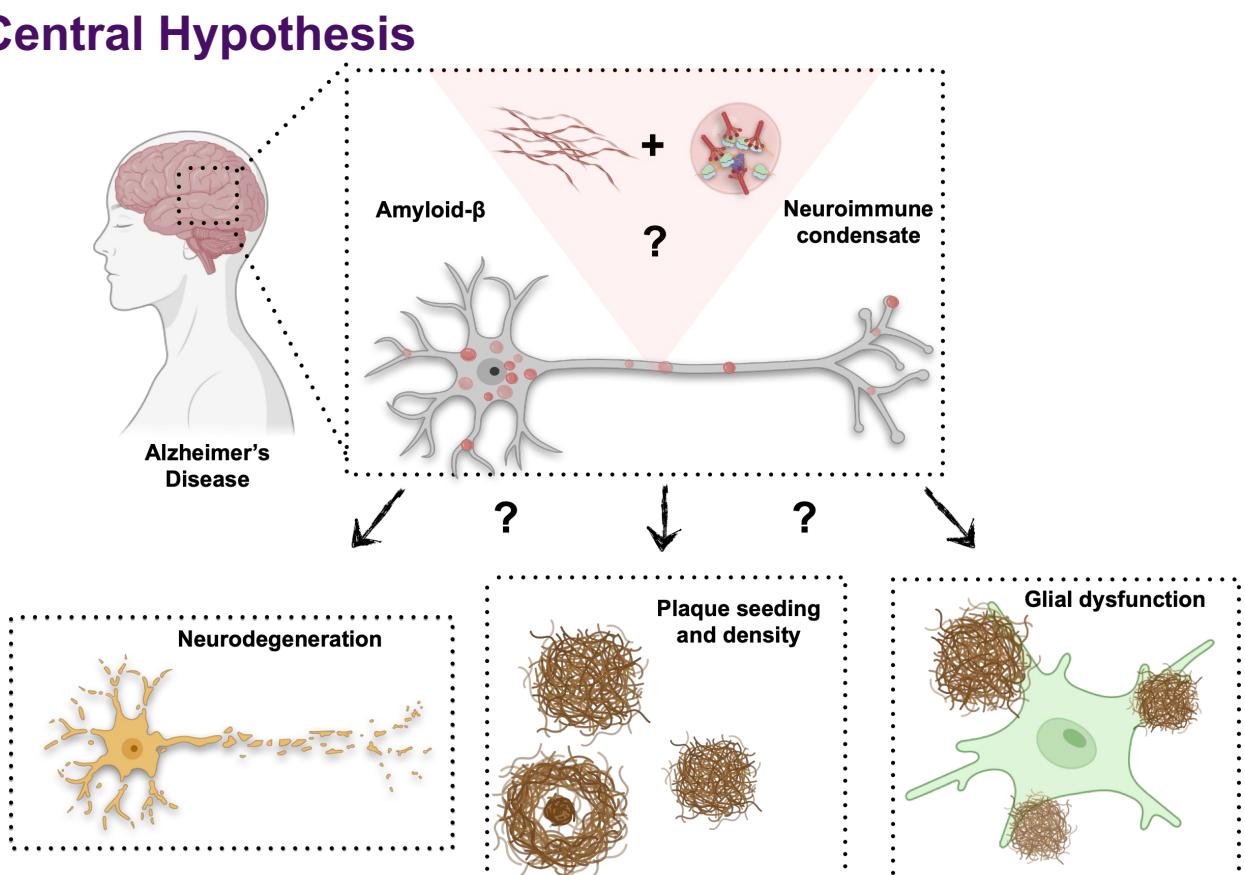
- Fibrillar amyloid-β (Aβ) disrupts C1q-RNA interactions and RNase sensitivity *in vitro*
- Extracellular Aβ plaques contain RNA that contributes to plaque density
- Degradation of RNA in extracellular Aβ plaques elevates insoluble protein content

INTRODUCTION

Neuroimmune mechanisms are increasingly implicated in Alzheimer’s disease (AD), with the complement cascade emerging as a key driver of synaptic and neuronal dysfunction. Complement proteins such as C1q and C3 mediate synapse loss in AD models and are elevated in patient biofluids and brain tissue, motivating therapeutic efforts targeting this pathway^{1,2}. The mechanisms underlying complement’s impact on neuronal function and its contribution to AD pathology remain incompletely understood. In the brain, C1q is produced primarily by microglia and exhibits context-dependent functions across development, aging, and disease, including roles in synaptic pruning. Our recent work identified an additional, previously unrecognized role for C1q in neuronal homeostasis. We demonstrated that C1q is internalized by neurons in the healthy adult brain, where it engages in RNA-dependent interactions with neuronal biomolecular condensates, thereby influencing proteostasis and translation during aging³. These findings revealed a previously unrecognized intracellular function for an immune protein in neurons and led to the discovery of a new class of structures we term ‘neuroimmune condensates.’

METHODS

Central Hypothesis



A. In vitro model: Fibrillar Amyloid β (Aβ)

Aβ fibrils (10μM) + C1q (1μg/ml) + RNA (1μg/ml) → **+/- RNase Image**

B. In vivo models

Alzheimer’s Disease

5X FAD: 3 mutations in APP, 2 mutations in PSEN1

Cryosection → **+/- RNase A (10μg/ml for 10')** → Stain & Image

RESULTS

Figure 1: Fibrillar Aβ disrupts C1q-RNA interactions

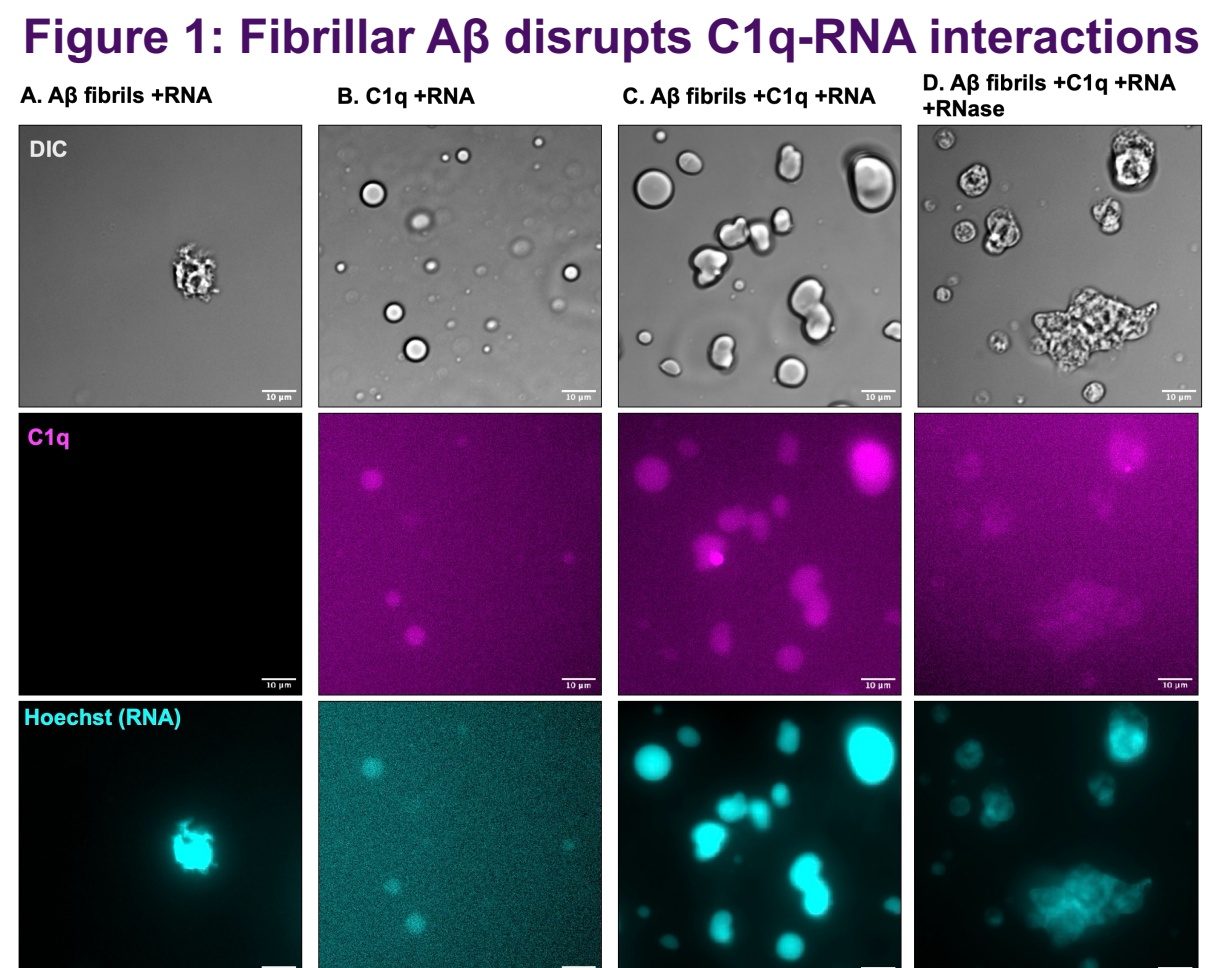


Figure 2: RNase treatment alters AD plaque density

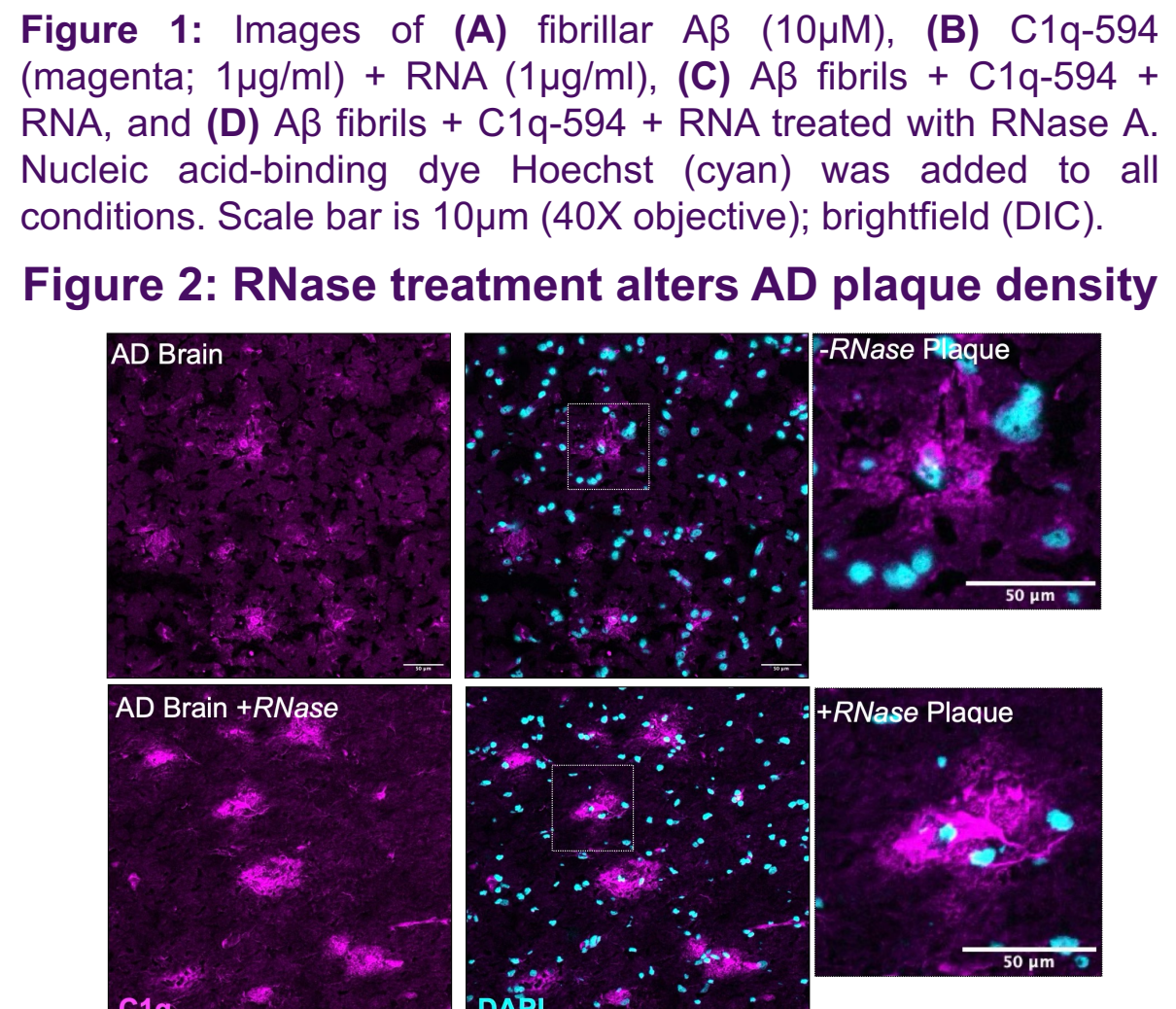
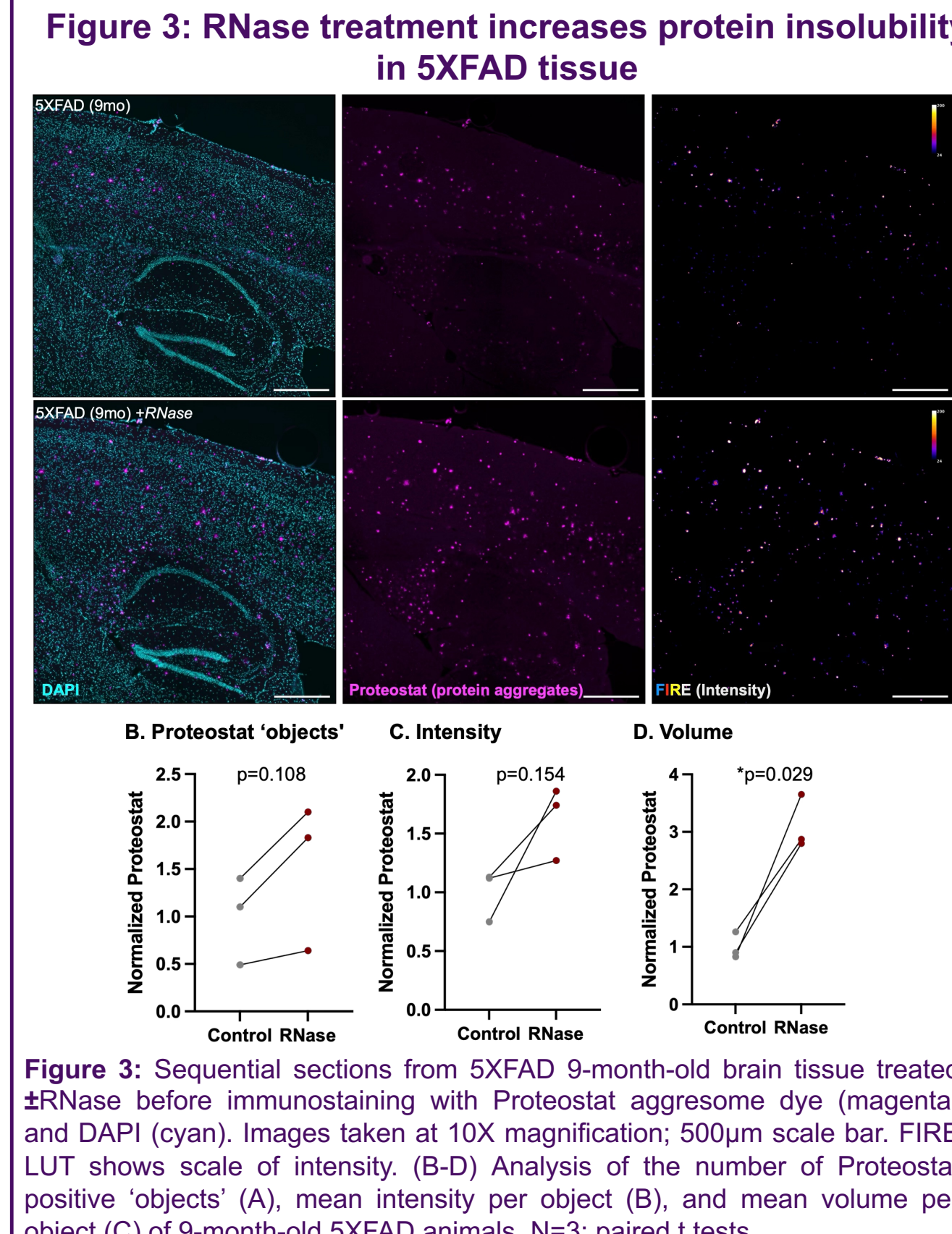
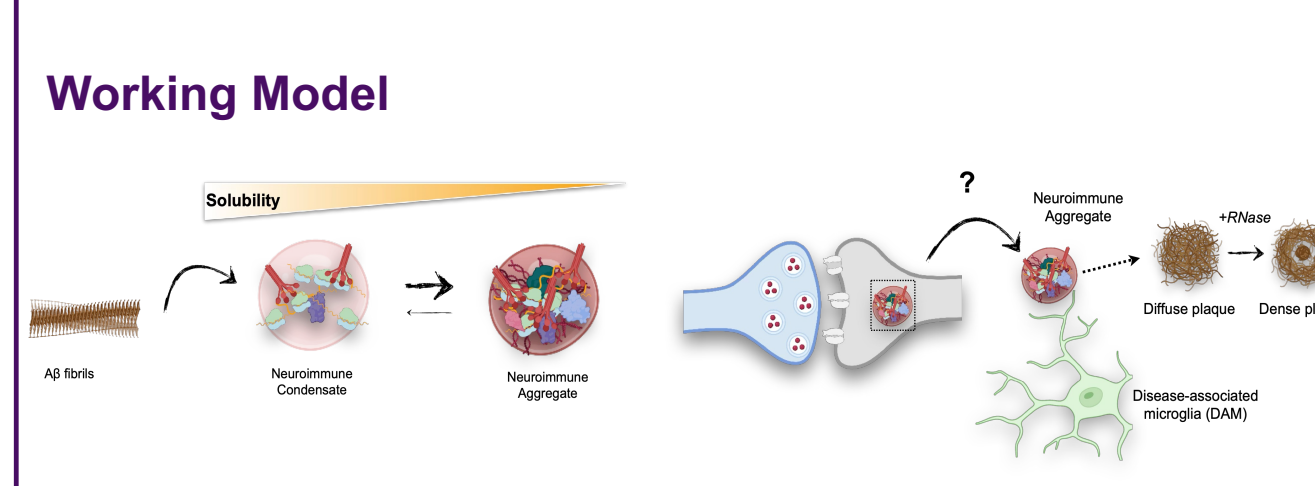


Figure 3: RNase treatment increases protein insolubility in 5XFAD tissue



Working Model



CONCLUSIONS

We propose that Aβ-mediated disruption of neuroimmune condensates generates RNA-containing aggregates that are released extracellularly, where they seed and shape plaque development and neuroinflammation. These studies will define how condensate biology intersects with neuroimmune signaling in AD, establish RNA as a functional component of extracellular Aβ plaques, and provide mechanistic insight into the impact of complement- and amyloid-targeted therapeutic strategies in AD.

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