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Role of extracellular vesicles in early synaptic dysfunction in AD

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Abstract

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder associated with amyloid-β (Aβ) and tau protein accumulation. Synaptic dysfunction is an early mechanism in AD which involves progressively larger areas of the brain over time. However how synaptic dysfunction starts and propagates is unknown. The hypothesis we are testing is that extracellular vesicles (EVs) released by microglia exposed to and carrying Aβ_{42} (Aβ-EVs) may be responsible for these early events in AD.

Method: Combining optical manipulation and time lapse imaging to place single EVs on RFP-positive cultured neuron dendrites and test their effects on the synapse, we show that Aβ-EVs rapidly alter dendritic spine morphology (a structural correlate of synaptic strength) locally at the site of interaction.

Result: Aβ-EVs induce a significant increase in the density of immature protrusions around the contact site (<7 µm from the contact point) starting 2 min after EV adhesion, compared to EVs released by microglia not exposed to Aβ_{42} (ctrl-EVs). Almost no alteration was detected far from the contact site (>60 µm).

Conclusion: Employing the same methodologies, we are currently monitoring Aβ-EV-neuron dynamics at the neuronal surface, to test whether Aβ-EVs may propagate dendritic spine alterations to adjacent regions over time, contributing to the spreading of synaptic deficits. Our data provide evidence of the involvement of microglial EVs in early synaptic dysfunction in AD, paving the way for novel therapeutic strategies.