

The role of Microglial Extracellular Vesicles in C1q-mediated Synaptic Pruning: insights from Extracellular Vesicles from Brain Tissue

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Production of C1q-storing EVs from WT microglia temporally correlates with the pruning period during postnatal development. C9orf72 KO microglia release more C1q-storing EVs compared to WT, and engulf more synapses in the hippocampus during the pruning period. Microglial EVs deliver C1q to pre-synapses and promote synaptic pruning *in vitro*. This study implicates abnormal EVs production from microglia in neurodevelopmental, neurodegenerative and age-related disorders characterized by dysregulated synaptic pruning.

INTRODUCTION

METHODS and RESULTS

GRAPHICAL ABSTRACT

The complement factor C1q is released by microglia, localizes on weak synapses and acts as a tag for **microglia-mediated synaptic pruning**, a fundamental process for proper circuit refinement across early postnatal life, reactivated in neurodegeneration and Alzheimer's disease. *How C1q tags synapses at specific times remains elusive.*

We explored the possible involvement of extracellular vesicles (EVs) released by microglia in C1q delivery to synapses designated for removal.

- Glial large EVs move at the neuron surface, scanning dendritic spines until they reach preferential contact sites *in vitro*.
- Complement factors are present at the surface of EVs.

EV isolation from mouse brain tissue

Microglial EVs carry C1q on their surface and increase when pruning activity is high.

Microglial EVs undergo preferential interactions with synapses and tag PRE-synapses with C1q

Microglial EVs promote synaptic pruning *in vitro* by acting on pre-synapses

Microglial EVs promote synaptic pruning: *in vivo* evidence

Working model

REFERENCE and CONTACT

D'Arrigo G, ..., Gabrielli M, Verderio C. Microglial Extracellular Vesicles Mediate C1q Deposition at the Pre-Synapse and Promote Synaptic Pruning. J Extracell Vesicles. 2025 Dec;14(12):e70173. doi: 10.1002/jev.2.70173. PMID: 41397032; PMCID: PMC12704692.

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CONCLUSIONS

Microglial EVs carry C1q on their surface, and deliver C1q to pre-synapses exposing phosphatidyl-serine (PS), thus promoting synaptic pruning. This study implicates abnormal EVs production from microglia in neurodevelopmental, neurodegenerative and age-related disorders characterized by dysregulated synaptic pruning.