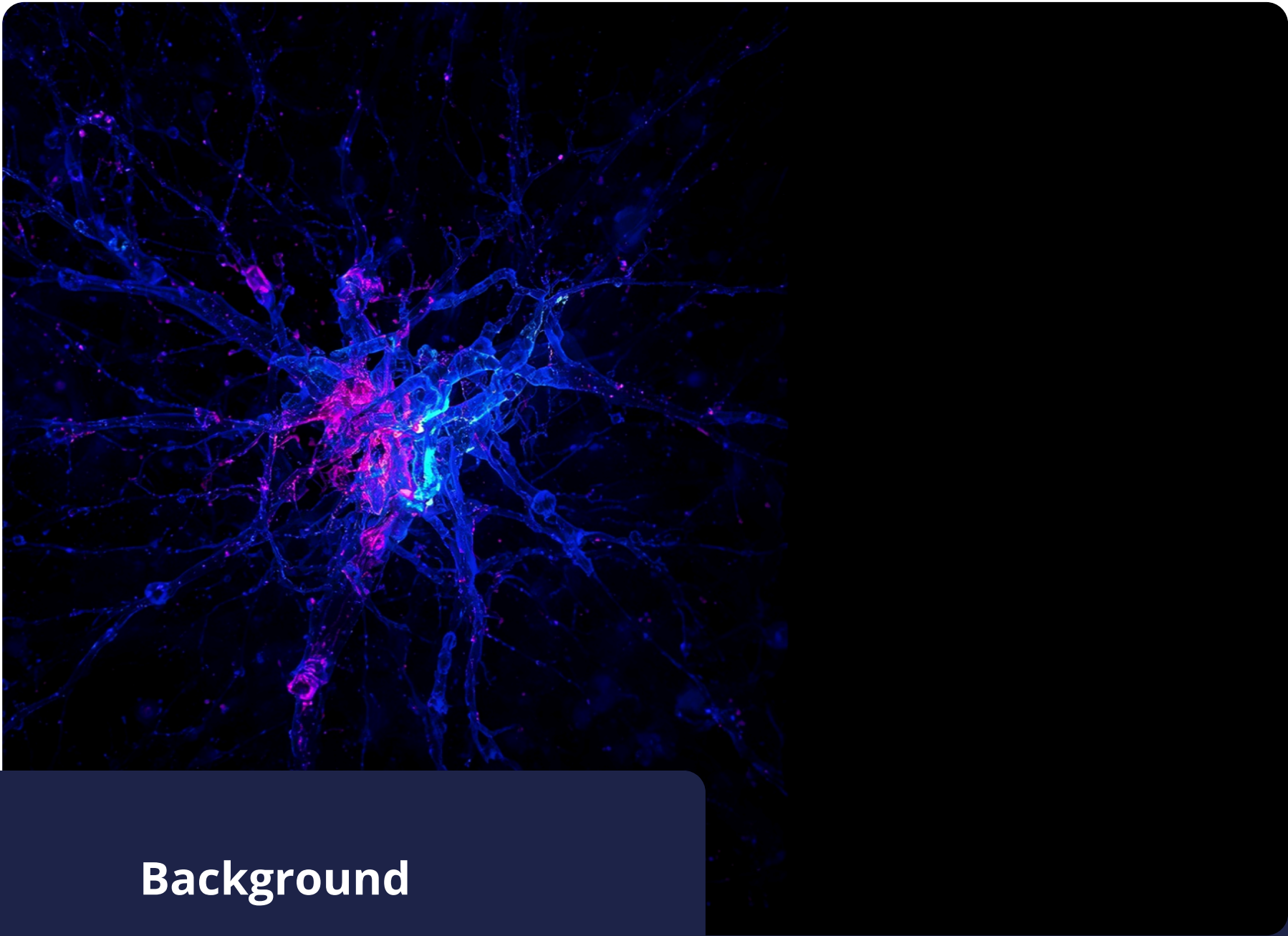
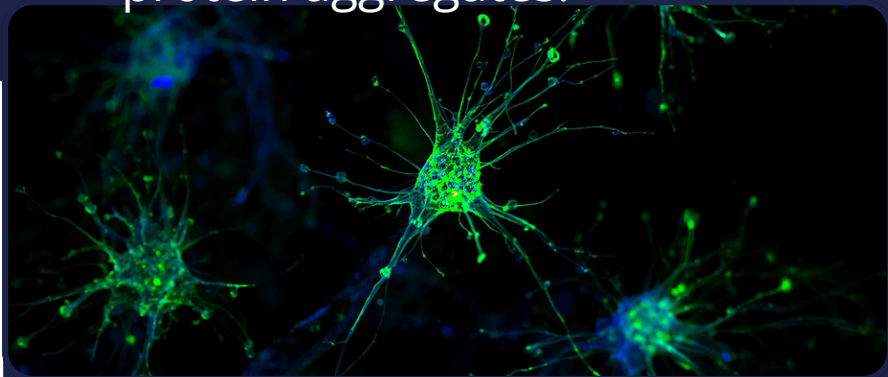




Background

- ✓ The "prion-like" propagation of misfolded alpha-synuclein (alpha-syn) is a defining feature of Parkinson's disease and related synucleinopathies.
- Historically, research focused on neuronal secretion and exosomal transport. Recent evidence identifies "zombosomes"—anucleated, motile, metabolically active bodies derived from astrocytes—as a major, previously overlooked vector.
- ✓ This review synthesizes current evidence regarding the biogenesis of zombosomes and their role in long-distance transmission of protein aggregates.



Research Question

Do astrocyte-derived zombosomes serve as active, high-capacity vectors for the long-distance transmission of alpha-synuclein pathology in neurodegeneration?

Methods

Literature Search

Comprehensive search across PubMed, Google Scholar, and bioRxiv through early 2024–2026.

Inclusion Criteria

Studies characterizing astrocytic-derived extracellular vesicles or anucleated cell fragments in proteinopathy contexts.

Thematic Analysis

Proteomic profile of zombosomes.
Role of glial stress in their formation.
Functional impact on recipient neuronal health.

Data Synthesis

Systematic thematic coding of included literature and cross-study validation.

Zombosomes as Active Vectors of Neurodegeneration: A Review of Astrocytic-Mediated alpha-Synuclein Spread

Keywords

- ✓ Zombosomes, Astrocytes, Alpha-Synuclein
- ✓ Neurodegeneration, Cerebral Organoids
- ✓ Parkinson's disease, Synucleinopathies, Extracellular Vesicles

Results & Discussion

Astrocytic-Mediated Spread

Zombosome Biogenesis

Astrocytes under proteotoxic stress shed anucleated motile bodies ~20x smaller than parent cells, retaining vimentin and active mitochondria but lacking genomic material.

Organoid Evidence

In 3D human cerebral organoids, zombosomes successfully infiltrate tissue and induce significant phosphorylated alpha-syn (p-alpha-syn) deposits.

Seeding Capacity

Human iPSC-derived cortical organoid studies show zombosomes from alpha-syn-exposed astrocytes transport phosphorylated alpha-syn, seeding ~10% of unexposed distant neurons within three days.

Post-Mortem Confirmation

Post-mortem human brain tissue confirms vimentin-positive, anucleated fragments in parenchyma of advanced neurodegeneration patients, validating clinical relevance.

Discussion

Zombosomes bridge the gap between passive extracellular vesicles and whole-cell migration, representing a distinct and active pathological courier mechanism.

Zombosome-mediated spread is a clinically relevant pathway in disease progression, offering a novel target distinct from classical exosomal or neuronal transmission routes.

Conclusions

Zombosomes represent a critical, "active" mechanism for systemic spread of neurodegeneration, shifting focus from neurons to astrocytic-mediated "zombie" couriers as therapeutic targets.

Future strategies may focus on inhibiting zombosome "shedding" or neutralizing their adhesive properties to halt disease progression at early stages.

Recommendations

Inhibiting astrocytic zombosome biogenesis or their adhesive surface properties represents a promising, novel therapeutic avenue for slowing alpha-syn spread in synucleinopathies.

Targeting the zombosome pathway may complement existing neuroprotective strategies and warrants urgent investigation in preclinical and clinical models.

Reference

- ✓ Dakhel A, Beretta C, Mothes T, et al. Zombosomes are anucleated cell couriers that spread alpha-synuclein pathology. Cell Rep. 2026 Jan 14;45(1):116831.

doi: 10.1016/j.celrep.2025.116831. Epub ahead of print. PMID: 41538327.