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Commentary

Extracellular Vesicle-Mediated Signal Transmission in Neurodegenerative Disorders: A Double-Edged Sword

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DESCRIPTION

Neurodegenerative disorders such as Alzheimer's Disease (AD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS) present profound clinical and societal challenges, particularly in high-income countries with aging populations. Despite extensive efforts, the underlying mechanisms of disease propagation and progression remain only partially understood. Recent research has brought Extracellular Vesicles (EVs) to the forefront as key players in intercellular communication within the nervous system. These nanoscale vesicles, including exosomes and microvesicles, have been implicated in both neuroprotection and neurodegeneration, suggesting a complex and context-dependent role in disease dynamics. Extracellular vesicles are membrane-bound carriers of molecular cargo proteins, lipids and various RNA species secreted by almost all cell types, including neurons, glia and endothelial cells. In the Central Nervous System (CNS), EVs serve as mediators of synaptic plasticity, neuronal survival and immune signaling. However, their ability to carry pathogenic proteins, such as amyloid-beta, tau, α-synuclein and TDP-43, raises the possibility that EVs also contribute to the spread of neurotoxic factors across brain regions. This dual functionality places EVs at a critical juncture in the pathogenesis of neurodegenerative diseases.

In Alzheimer's disease, EVs have been found to contain Amyloid Precursor Protein (APP) and its cleavage products, including amyloid-beta peptides. These vesicles can travel extracellularly and transfer their contents to neighboring neurons or microglia, potentially amplifying amyloid plaque formation and associated inflammation. Similarly, in tauopathies, EVs have been shown to mediate the intercellular transfer of hyperphosphorylated tau, accelerating its aggregation in recipient cells. This mechanism may explain the stereotyped progression of tau pathology across specific neural circuits. In Parkinson's disease, EVs derived from dopaminergic neurons have been observed to carry misfolded α-synuclein, which can seed aggregation in healthy neurons. Microglial-derived EVs also contribute to neuroinflammation, creating a feedback loop that exacerbates neuronal damage. Interestingly, EVs may not only carry pathological proteins but also modulate gene expression in target cells through their RNA cargo, including microRNAs (miRNAs). For example, miR-21 and miR-124, enriched in neuronal EVs, have been shown to influence inflammatory signaling and synaptic function, which are often dysregulated in PD and AD.

On the other hand, EVs also have protective and regenerative roles. Neural stem cells and astrocytes release EVs enriched in neurotrophic factors and anti-inflammatory miRNAs that can promote neuronal survival and repair. EVs have been shown to cross the Blood-Brain Barrier (BBB), making them promising candidates for biomarkers and therapeutic delivery vehicles. Their ability to reflect the molecular state of their parent cells allows for early detection of disease-specific signatures in accessible biofluids like cerebrospinal fluid or blood. Several studies are exploring EV-derived biomarkers for early diagnosis and progression tracking in AD and ALS.

Despite these promising findings, there are significant challenges in translating EV research into clinical practice. Isolation and characterization techniques for EVs remain inconsistent, and distinguishing between vesicle subtypes is difficult due to overlapping size and marker profiles. Moreover, while EVs can facilitate the spread of pathology, their exact role whether causative or correlative remains under investigation. There is also a need to better understand how EV content is selectively packaged and whether this process can be manipulated therapeutically.

Therapeutic strategies targeting EVs are emerging. One approach involves inhibiting EV biogenesis or release to prevent the spread of neurotoxic proteins. Another focuses on engineering EVs to carry therapeutic molecules such as siRNAs, anti-inflammatory agents, or even gene-editing tools like CRISPR-Cas9. The natural stability, biocompatibility and ability of EVs to cross biological barriers make them attractive vehicles for CNS drug delivery. Yet, such approaches require fine-tuned control to avoid disrupting physiological EV functions that are beneficial to neural health.

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CONCLUSION

Extracellular vesicles represent a critical but complex mechanism of signal transmission in the brain, capable of both mitigating and propagating neurodegenerative processes. Their involvement in transporting pathological proteins, RNAs and regulatory molecules across neural networks provides valuable insight into the progression of diseases like Alzheimer's, Parkinson's and ALS. At the same time, their protective and reparative functions point to their potential as tools for diagnosis and therapy. As research into EV biology advances, it will be essential to dissect the dual roles of these vesicles and develop strategies that selectively enhance their beneficial effects while limiting their harmful contributions. Precision targeting, standardized isolation protocols and deeper understanding of EV content selection will be key. If harnessed effectively, EVs could play a transformative role in the management of neurodegenerative disorders, shifting the paradigm from symptomatic treatment to mechanism-based intervention and early diagnosis.