



EXTRACELLULAR VESICLES IN THE CENTRAL NERVOUS SYSTEM: INTERCELLULAR COMMUNICATION, DISEASE PROPAGATION, AND THERAPEUTIC POTENTIAL

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Abstract

Extracellular vesicles (EVs), including exosomes and microvesicles, are membrane-bound particles released by essentially all cell types that carry proteins, lipids, and nucleic acids capable of modifying the function of recipient cells. Within the central nervous system, EVs derived from neurons, astrocytes, oligodendrocytes, and microglia participate in normal intercellular communication, including metabolic support of axons, synaptic modulation, and myelin maintenance. Under pathological conditions, however, EVs can serve as vehicles for the cell-to-cell propagation of misfolded proteins, including amyloid-beta, tau, and alpha-synuclein, contributing to the spread of pathology in neurodegenerative disease. EVs also cross the blood-brain barrier and appear in cerebrospinal fluid and peripheral blood,



positioning them as promising biomarkers and as engineered vehicles for targeted drug delivery to the brain. This review summarizes the biogenesis and physiological roles of EVs in the nervous system, their role in the propagation of neurodegenerative pathology, their relevance to major neurological disorders, and emerging diagnostic and therapeutic applications.

Keywords: Extracellular vesicles, Exosomes, Intercellular communication, Prion-like propagation, Alpha-synuclein, Tau, Biomarkers

1. Introduction and Biogenesis of Extracellular Vesicles

Extracellular vesicles are a heterogeneous group of membrane-enclosed particles released by cells into the extracellular space, broadly classified according to their biogenesis into exosomes, generated within the endosomal system, and microvesicles, which bud directly from the plasma membrane. Exosome formation begins with inward budding of the endosomal membrane to generate intraluminal vesicles within multivesicular bodies, a process regulated by the endosomal sorting complex required for transport (ESCRT) machinery as well as ESCRT-independent mechanisms involving ceramide (Colombo, Raposo, & Théry, 2014). Multivesicular bodies subsequently fuse with the plasma membrane, releasing their intraluminal vesicles as exosomes in a process regulated by small GTPases including Rab27a and Rab27b. Once released, EVs carry a molecular cargo reflecting their cell of origin, including membrane and cytosolic proteins, lipids, messenger RNA, and microRNA, which can be transferred to and functionally alter recipient cells (Valadi et al., 2007). This capacity to transfer functional biological material between cells, without requiring direct cell-cell contact or classical secreted signaling molecules, has established EVs as a distinct and important mode of intercellular communication, particularly relevant within the densely packed and functionally interdependent cellular environment of the central nervous system.

2. Extracellular Vesicles in Normal CNS Intercellular Communication



Within the healthy nervous system, EVs released by neurons, astrocytes, oligodendrocytes, and microglia contribute to numerous physiological processes. Oligodendrocyte-derived exosomes are released in an activity-dependent manner, triggered by neuronal glutamate signaling through NMDA and AMPA receptors on the oligodendrocyte surface, and are subsequently internalized by neurons, where they support axonal energy metabolism and stress resistance, providing a direct mechanistic link between myelinating glia and the axons they ensheath (Frühbeis et al., 2013). Astrocyte-derived EVs have been implicated in synaptic plasticity, neuroprotection, and the transfer of trophic factors to neurons under conditions of metabolic stress. Neurons themselves release EVs in an activity-dependent manner from presynaptic terminals, where they may participate in synaptic remodeling and the local regulation of protein composition. Microglia-derived EVs contribute to intercellular signaling relevant to immune surveillance and can modulate neuronal excitability. Collectively, these observations indicate that EV-mediated communication is a normal and physiologically important feature of neuron-glia interaction, operating alongside classical synaptic and paracrine signaling mechanisms to support neuronal metabolism, myelin maintenance, and network homeostasis.

3. Extracellular Vesicles as Vehicles for Prion-like Protein Propagation

A major pathological role attributed to EVs in the central nervous system is their capacity to mediate the cell-to-cell transfer of misfolded, aggregation-prone proteins, contributing to the progressive spread of pathology characteristic of several neurodegenerative diseases. Amyloid-beta peptide has been shown to be generated within multivesicular bodies and released in association with exosomes, with exosomal amyloid-beta capable of seeding aggregation in recipient cells (Rajendran et al., 2006). Similarly, alpha-synuclein can be packaged into EVs and released by neurons, providing a mechanism by which misfolded alpha-synuclein aggregates



may transfer between anatomically connected neurons, contributing to the stereotyped spatial progression of pathology observed in Parkinson's disease (Danzer et al., 2012). Tau protein has likewise been identified within neuronally derived EVs, and exosome-associated tau has been shown to be taken up by recipient neurons and to seed intracellular tau aggregation, supporting a similar prion-like mechanism of trans-synaptic spread in Alzheimer's disease and related tauopathies. In each of these examples, EVs are proposed to protect their aggregation-prone protein cargo from extracellular degradation while facilitating efficient, targeted delivery into recipient cells via endocytic uptake, thereby providing a plausible cellular mechanism for the network-based spreading patterns of neurodegenerative pathology observed on human neuroimaging and neuropathological staging.

4. EVs in Neurodegenerative and Neurological Diseases

In Alzheimer's disease, neuronally derived EVs isolated from patient plasma have been shown to carry elevated levels of pathological forms of amyloid-beta and phosphorylated tau, with alterations detectable years before clinical diagnosis, suggesting that EV cargo may reflect early molecular changes within the diseased brain (Fiandaca et al., 2015). In Parkinson's disease, EVs isolated from cerebrospinal fluid and plasma have been found to contain oligomeric alpha-synuclein, and EV-associated alpha-synuclein has been proposed to contribute to both disease propagation and to serve as a candidate biomarker for diagnosis and disease staging. In amyotrophic lateral sclerosis, EVs derived from glial cells carrying mutant superoxide dismutase 1 (SOD1) have been shown to be toxic to motor neurons in experimental models, suggesting a role for glial-to-neuron EV signaling in non-cell-autonomous motor neuron injury. Following traumatic brain injury, plasma EV levels and cargo composition change acutely, and EVs released from injured neurons and activated glia may contribute to secondary inflammatory injury while also



offering a potential minimally invasive window into ongoing pathological processes within the injured brain.

5. Diagnostic and Therapeutic Applications

Because EVs cross the blood-brain barrier and can be isolated from cerebrospinal fluid, blood, and other accessible body fluids, they represent an attractive source of minimally invasive biomarkers for neurological disease. Neuron-derived EVs can be enriched from peripheral blood using surface markers such as L1CAM, allowing indirect sampling of brain-derived molecular cargo without invasive tissue biopsy, an approach that has been applied to detect early molecular signatures of Alzheimer's disease in plasma (Fiandaca et al., 2015). Beyond diagnostics, EVs are being explored as engineered delivery vehicles for therapeutic cargo. Because EVs are capable of natural blood-brain barrier crossing, engineered exosomes displaying targeting peptides on their surface have been used experimentally to deliver small interfering RNA (siRNA) to the brain following systemic administration, achieving gene knockdown in neurons, microglia, and oligodendrocytes without inducing significant immune activation or toxicity (Alvarez-Erviti et al., 2011). This capacity positions EVs as a potential platform for delivering nucleic acid therapeutics, small molecules, or neuroprotective proteins across the blood-brain barrier, addressing one of the central limitations in central nervous system pharmacotherapy. However, substantial challenges remain regarding large-scale, reproducible EV production, cargo-loading efficiency, targeting specificity, and long-term safety, all of which must be resolved before EV-based diagnostics and therapeutics can be widely adopted in clinical practice.

Conclusion

Extracellular vesicles represent a fundamental, and until recently underappreciated, mode of intercellular communication within the central nervous system, supporting normal neuron-glia interactions while also serving as vehicles



for the cell-to-cell propagation of misfolded proteins in neurodegenerative disease. Their presence in accessible body fluids and their capacity to cross the blood-brain barrier have positioned EVs as promising tools for both the early detection of neurological disease and the targeted delivery of therapeutic agents to the brain. Continued elucidation of the mechanisms governing EV biogenesis, cargo selection, and cellular uptake, alongside the development of standardized isolation and engineering methods, will be essential for translating the biological promise of extracellular vesicles into clinically useful diagnostic and therapeutic tools.

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