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Unlocking the Potential of Non-Neuronal Cell-Derived Extracellular Vesicles in Pain Relief and Neuroprotection

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INTRODUCTION & AIM

- Extracellular vesicles (EVs), including exosomes, are gaining recognition as crucial mediators of intercellular communication.
- These nanosized vesicles facilitate the transfer of bioactive molecules such as microRNAs, proteins, and lipids, influencing diverse physiological and pathological processes.
- In the nervous system, EVs derived from non-neuronal glial cells, including Schwann cells, oligodendrocytes, and satellite glial cells (SGCs), exhibit distinct neuroprotective and analgesic properties.
- Recent research highlights the potential of these glial-derived EVs in modulating neuroinflammation, promoting neuronal repair, and regulating pain signaling pathways.
- By influencing key mechanisms underlying chronic pain and nerve damage, these vesicles present a promising, cell-free therapeutic strategy for neuroprotection and pain management.
- This study aims to explore the functional roles and therapeutic potential of glial cell-derived EVs in neural repair and chronic pain modulation, advancing our understanding of their mechanisms and translational applications.

METHOD

A scoping review was conducted to systematically explore the role of extracellular vesicles (EVs) derived from Schwann cells, oligodendrocytes, and satellite glial cells (SGCs) in neuroprotection and pain modulation.

Literature Search & Selection

A comprehensive search was performed in PubMed, Scopus, and Web of Science databases to identify relevant studies published up to November 2024. Search terms included combinations of "extracellular vesicles," "exosomes," "Schwann cells," "oligodendrocytes," "satellite glial cells," "neuroprotection," and "chronic pain.“

Screening & Inclusion Criteria

Titles and abstracts were screened for relevance.

Full-text articles were assessed for eligibility.

Inclusion criteria:

- Studies investigating EVs from Schwann cells, oligodendrocytes, or SGCs
- Research focusing on EV cargo, functional roles, or therapeutic applications
- Peer-reviewed primary research articles in English

Exclusion criteria:

Studies lacking experimental data, review articles, and those focusing on non-glial-derived EVs.

Data Extraction & Analysis

- Key information was extracted from 15 selected studies, including: EV cargo composition (microRNAs, proteins, lipids)
- Functional mechanisms (modulation of inflammation, neuroprotection, pain signaling)
- Therapeutic implications (potential for chronic pain management and neural repair)

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RESULTS & DISCUSSION

- Our analysis reveals that extracellular vesicles (EVs) derived from Schwann cells, oligodendrocytes, and satellite glial cells (SGCs) exhibit distinct but complementary roles in neuroprotection, pain modulation, and neuronal repair.
- These EVs carry a diverse range of microRNAs, proteins, and lipids that contribute to their therapeutic potential.

Schwann Cell-Derived EVs:

Neuroprotection & Pain Modulation: Schwann cell-derived EVs are highly enriched with neuroprotective microRNAs such as miR-21 and miR-146a, which regulate inflammatory pathways, suppress neuroinflammation, and enhance neuronal survival. Additionally, these EVs transport key neurotrophic factors, including brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), both of which promote neuronal repair and functional recovery. The presence of these bioactive molecules suggests that Schwann cell EVs play a crucial role in reducing pain and supporting axonal regeneration in neuropathic conditions.

Oligodendrocyte-Derived EVs:

Myelin Integrity & Oxidative Stress Reduction: EVs from oligodendrocytes carry structural proteins such as myelin basic protein (MBP) and proteolipid protein (PLP), which are essential for maintaining myelin integrity and facilitating neuronal repair. Additionally, they are rich in superoxide dismutase (SOD), a powerful antioxidant enzyme that mitigates oxidative stress, protecting neurons from further damage. These properties highlight their potential role in treating demyelinating diseases and enhancing neuroprotection.

SGC-Derived EVs:

Inflammation & Pain Modulation: SGC-derived EVs share similarities with Schwann cell EVs, carrying miR-21 and miR-146a, but they exhibit a unique role in modulating neuronal hyperexcitability and pain signaling. Their cargo includes anti-inflammatory cytokines such as interleukin-10 (IL-10), which exerts potent immunomodulatory effects by reducing pro-inflammatory responses. This highlights their potential to attenuate chronic pain conditions by directly influencing peripheral and central pain pathways.

Key Molecular Cargo and Functions of Glial-Derived EVs

Glial Cell Type	Key Cargo	Functions
Schwann Cells	miR-21, miR-146a, BDNF, NGF	Regulates inflammation, promotes neuronal survival, enhances repair
Oligodendrocytes	MBP, PLP, SOD	Maintains myelin integrity, reduces oxidative stress, supports neuronal repair
Satellite Glial Cells (SGCs)	miR-21, miR-146a, IL-10	Modulates neuronal hyperexcitability, reduces inflammation, attenuates pain

CONCLUSION & FUTURE WORK

Our findings highlight the therapeutic potential of glial-derived EVs as innovative, cell-free tools for chronic pain management and neural regeneration. However, several key research gaps remain, including 1) standardization of EV isolation and characterization methodologies to improve reproducibility and clinical translation; 2) deeper molecular profiling of EV cargo to understand their precise mechanisms of action; and 3) preclinical and clinical studies to validate their therapeutic efficacy and safety for neurological disorders.

Future research should focus on refining EV-based therapeutic strategies and exploring their potential for clinical applications.