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Research Paper

M2 microglia-derived extracellular vesicles promote white matter repair and functional recovery via miR-23a-5p after cerebral ischemia in mice

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Abstract

Rationale: White matter repair is critical for the cognitive and neurological functional recovery after ischemic stroke. M2 microglia are well-documented to enhance remyelination and their extracellular vesicles (EVs) mediate cellular function after brain injury. However, whether M2 microglia-derived EVs could promote white matter repair after cerebral ischemia and its underlying mechanism are largely unknown.

Methods: EVs were isolated from IL-4 treated microglia (M2-EVs) and untreated microglia (M0-EVs). Adult ICR mice subjected to 90-minute transient middle cerebral artery occlusion received intravenous EVs treatment for seven consecutive days. Brain atrophy volume, neurobehavioral tests were examined within 28 days following ischemia. Immunohistochemistry, myelin transmission electron microscope and compound action potential measurement were performed to assess white matter structural remodeling, functional repair and oligodendrogenesis. The effects of M2-EVs on oligodendrocyte precursor cells (OPCs) were also examined *in vitro*. EVs' miRNA sequencing, specific miR-23a-5p knockdown in M2-EVs and luciferase reporter assay were used to explore the underlying mechanism.

Results: M2-EVs reduced brain atrophy volume, promoted functional recovery, oligodendrogenesis and white matter repair *in vivo*, increased OPC proliferation, survival and differentiation *in vitro*. miR-23a-5p was enriched in M2-EVs and could promote OPC proliferation, survival and maturation, while knocking down miR-23a-5p in M2-EVs reversed the beneficial effects of M2-EVs both *in vitro* and *in vivo*. Luciferase reporter assay showed that miR-23a-5p directly targeted Olig3.

Conclusion: Our results demonstrated that M2 microglia could communicate to OPCs through M2-EVs and promote white matter repair via miR-23a-5p possibly by directly targeting Olig3 after ischemic stroke, suggesting M2-EVs is a novel and promising therapeutic strategy for white matter repair in stroke and demyelinating disease.

Key words: extracellular vesicles; ischemia; microglia; oligodendrocyte precursor cells; white matter

Introduction

Stroke is a life threatening disease globally with high morbidity, mortality, healthcare costs and limited therapies [1, 2]. Ischemic stroke, accounting for more than 80% of stroke, causes not only gray matter but also remarkable white matter injury, since white matter is more vulnerable to ischemia than gray