Exosomal MicroRNAs from Mesenchymal Stem/stromal Cells: Biology and Applications in Neuroprotection

Aida Nasirishargh, Priyadarsini Kumar, Lalithasri Ramasubramanian, Kaitlin Clark, Dake Hao, Sabrina Valentina Lazar, and Aijun Wang.
Department of Surgery, School of Medicine, University of California Davis, Sacramento, CA 95817

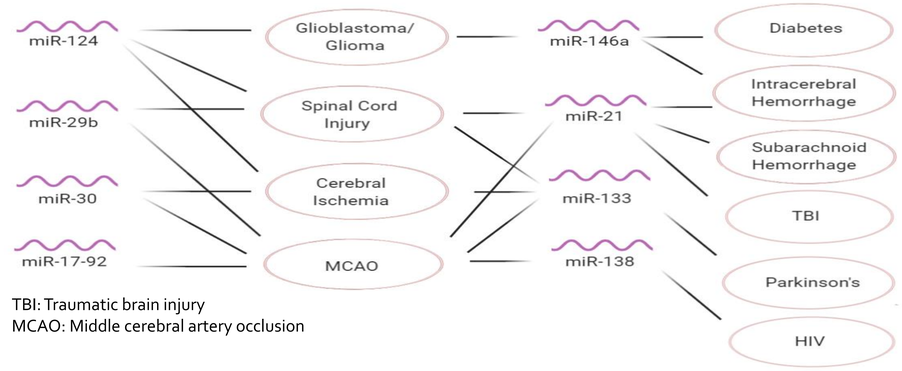
Introduction and Method

- Mesenchymal stem (MSCs) are extensively studied as cell-therapy agents for neurological diseases.
- Recent studies consider exosomal microRNAs secreted by MSCs as important mediators for MSCs' neuroprotective functions.
- Exosomal miRNAs have significant therapeutic potential for neurological disorders such as stroke, traumatic brain injury, and neuroinflammatory or neurodegenerative diseases.
- This review discusses the neuroprotective effects of selected miRNAs (miR-21, miR-17-92, miR-133, miR-138, miR-124, miR-30, miR146a, and miR-29b) and explores their mechanisms of action for the treatment of various neurological diseases.
- It also provides an overview of bioengineering approaches for isolating exosomes, optimizing their yield and manipulating the miRNA content of their cargo.
- English language studies on neuroprotective MSC-derived exosomal miRNAs were located through PubMed online search using the keywords "Mesenchymal stem cell (MSC)," "exosomal miRNA," "neuroprotective," "biotherapy," and "engineered exosomes." This review included all papers current to the end of August 2020 and did not exclude studies on the basis of methodological flaws.

Techniques used to manipulate the content of MSCs and their exosomes.

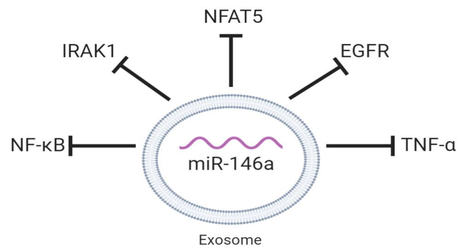
Technique	Description	Exosomal loading
Transfection	A lentiviral vector or a plasmid is encoded with the desired miRNA and introduced to the MSCs.	Indirect
Electroporation	Electrical pulses are applied to cause a temporary loss of the stability of the membranes of both MSCs and exosomes, allowing for cargo loading.	Direct and indirect
Sonication	Low-frequency ultrasound is applied to disrupt the membrane integrity of the exosomes to allow transferring small RNAs into the exosomes.	Direct
Modified $CaCl_2$ Transfection	Phosphate-buffered saline is mixed with a $CaCl_2$ solution containing the desired small RNA. RNA–calcium phosphate precipitates on the cell/exosomes surface. A heat shock changes the fluidity of the exosomes' plasma membranes for introducing.	Direct
Co-incubation of exosome with hydrophobically modified RNA	Conjugating the small RNA with a cholesterol moiety and allows for diffusing the exosomal membrane during simple incubation.	Direct

Therapeutic potential of MSC-derived miRNAs for neurological disorders.

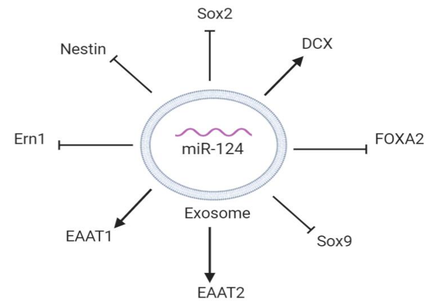


TBI: Traumatic brain injury
MCAO: Middle cerebral artery occlusion

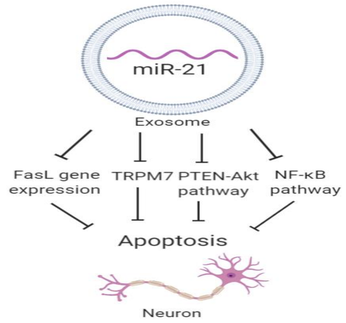
Exosomal miR-146a's Neuroprotective pathways



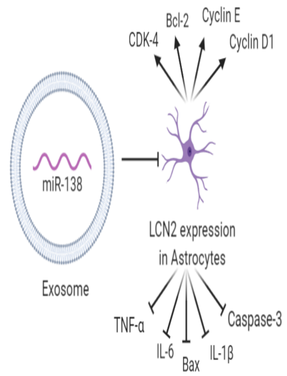
Exosomal miR-124's Neuroprotective pathways



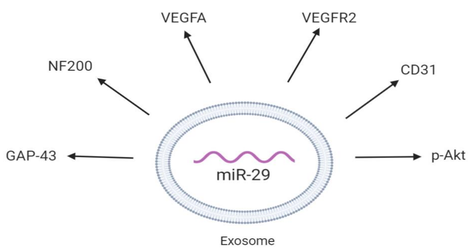
Exosomal miR-21's Neuroprotective pathways



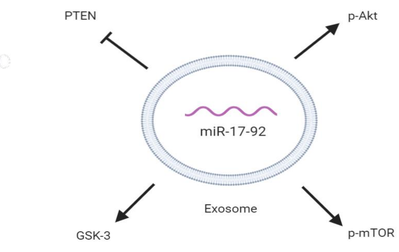
Exosomal miR-138's Neuroprotective pathways



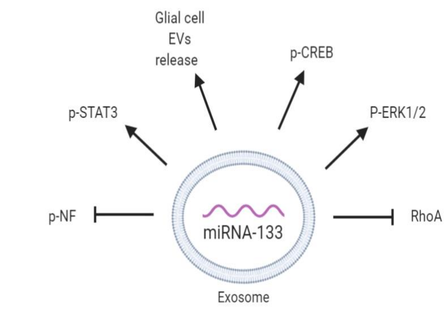
Exosomal miR-29's Neuroprotective pathways



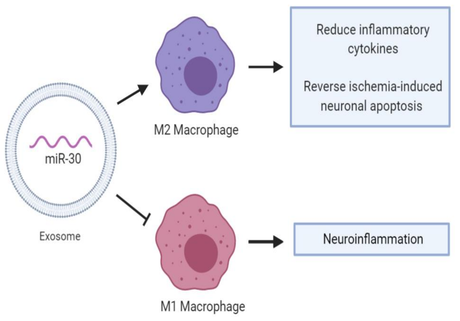
Exosomal miR-17-92's Neuroprotective pathways



Exosomal miR-133's Neuroprotective pathways



Exosomal miR-30's Neuroprotective pathways



Discussion

- Bone marrow-MSCs are most widely studied for MSC treatments. Limited research has been done on the therapeutic potential of neuroprotective miRNAs that are abundant in MSCs derived from other types of tissues, such as the placenta and peripheral blood.
- Some neuroprotective miRNAs that are abundant in MSCs have received limited attention for their functions as exosomal miRNAs.
- There is a gap in knowledge for the clinical implications of exosomal miRNA treatments. A clinical trial that used BM-MSC-derived exosomes enriched in miR-124 in five patients with acute ischemic stroke has been reported by Clinicaltrials.gov . No result for this trial has been published so far.