Review

Potential effects of mesenchymal stem cell derived extracellular vesicles and exosomal miRNAs in neurological disorders

https://doi.org/10.4103/1673-5374.313026

Date of submission: September 5, 2020

Date of decision: November 23, 2020

Date of acceptance: January 18, 2021

Date of web publication: April 23, 2021

Masako Nakano*, Mineko Fujimiya

Abstract

Mesenchymal stem cells are multipotent cells that possess anti-inflammatory, anti-apoptotic and immunomodulatory properties. The effects of existing drugs for neurodegenerative disorders such as Alzheimer's disease are limited, thus mesenchymal stem cell therapy has been anticipated as a means of ameliorating neuronal dysfunction. Since mesenchymal stem cells are known to scarcely differentiate into neuronal cells in damaged brain after transplantation, paracrine factors secreted from mesenchymal stem cells have been suggested to exert therapeutic effects. Extracellular vesicles and exosomes are small vesicles released from mesenchymal stem cells that contain various molecules, including proteins, mRNAs and microRNAs. In recent years, administration of exosomes/extracellular vesicles in models of neurological disorders has been shown to improve neuronal dysfunctions, via exosomal transfer into damaged cells. In addition, various microRNAs derived from mesenchymal stem cells that regulate various genes and reduce neuropathological changes in various neurological disorders have been identified. This review summarizes the effects of exosomes/extracellular vesicles and exosomal microRNAs derived from mesenchymal stem cells on models of stroke, subarachnoid and intracerebral hemorrhage, traumatic brain injury, and cognitive impairments, including Alzheimer's disease.

Key Words: exosomes; extracellular vesicles; mesenchymal stem cells; microRNA; neurological disorders

Introduction

Mesenchymal stem cells (MSCs) are multipotent progenitor cells that can be isolated from several tissues, including bone marrow (BM), adipose tissue, umbilical cord (UC) and placenta (Heo et al., 2016). Since these cells exert anti-inflammatory, anti-apoptotic and immunomodulatory effects, MSCs have been used in clinical trials for a wide range of diseases, including neurodegenerative diseases (Saeedi et al., 2019). The initial hypothesis was that MSCs would readily differentiate into neurons or other cells in the damaged brain after transplantation. However, only limited numbers of MSCs have been shown to undergo such differentiation, and the paracrine factors secreted from MSCs are now suggested to exert therapeutic effects, rather than the actual differentiation of MSCs (Nooshabadi et al., 2018). All type of MSCs including BM-MSCs, adipose-derived (AD)-MSCs and UC-MSCs show the common surface makers, such as CD29, CD44, CD73 and CD90 (Heo et al., 2016). However BM-MSCs are known to exert immunosuppressive activity because they secrete higher level of cytokines like interleukin-10 (IL-10) and transforming growth factor beta 1 more than other types of MSCs (Heo et al., 2016).

Extracellular vesicles (EVs) are vesicles secreted from various cell types, including MSCs. EVs contain molecules such as DNA, mRNA, microRNA (miRNA) and proteins (Lai et al., 2014). EVs are classified into three types: exosomes (40–100 nm), microvesicles (100–1000 nm) and apoptotic bodies (50–4000 nm) (Lai et al., 2014). EVs transfer their cargo of molecules into recipient cells, thus acting as a means of intercellular communication. Thus, in contrast to cellular miRNAs that localize within cells, EV containing miRNAs can be transferred into other cells and affect the function of recipient cells (Lai et al., 2014). As noncoding RNA of 19–24 nucleotides, miRNAs regulate the expression of up to 30% of protein-coding genes (Bhaskaran and Mohan, 2014). Since miRNAs suppress the expression of various target genes, therapeutic effects of MSCs might be largely exerted through the transfer of miRNAs via EVs.

This review focuses on the effects of MSC-derived exosomes/EVs on various models of neurological disorder. We also summarize the main miRNAs derived from exosomes that ameliorate the pathological changes seen in each brain disease. Recently, a number of miRNAs derived from MSCs have been identified as effective against various neurological disorders (**Figure 1**). A PubMed search was conducted using the keywords "mesenchymal stem cells", "exosomes", "extracellular vesicles", "miRNA" and "brain" for the period from 2010 to 2020. In this paper, we review the effects of exosomes/EVs and exosomal miRNAs derived from MSCs on models of stroke, subarachnoid hemorrhage (SAH), intracerebral hemorrhage, traumatic brain injury (TBI), cognitive impairments and other neurological disorders.

Department of Anatomy, Sapporo Medical University School of Medicine, Sapporo, Hokkaido, Japan

*Correspondence to: Masako Nakano, MD, PhD, m.nakano@sapmed.ac.jp.

https://orcid.org/0000-0003- 1025-2386 (Masako Nakano)

How to cite this article: *Nakano M, Fujimiya M (2021) Potential effects of mesenchymal stem cell derived extracellular vesicles and exosomal miRNAs in neurological disorders. Neural Regen Res 16(12):2359-2366.*

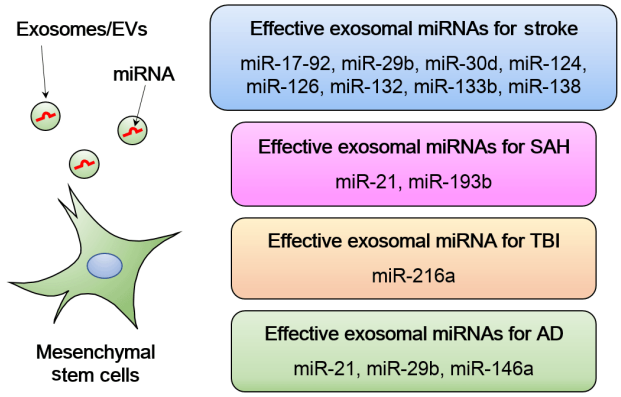

Figure 1 | Schema of mesenchymal stem cell derived exosomes/EVs and effective exosomal miRNAs in neurological disorders.
Mesenchymal stem cells secrete exosomes and responsible miRNAs that exert beneficial effects are shown. AD: Alzheimer's disease; EVs: extracellular vesicles; SAH: subarachnoid hemorrhage; TBI: traumatic brain injury.

Effects of Exosomes/Extracellular Vesicles and Exosomal MicroRNAs Derived from Mesenchymal Stem Cells on Stroke Models

Exosomes/EVs secreted from several kinds of MSCs, such as BM-MSCs, AD-MSCs, and UC-MSCs, are known to improve neuronal functions in stroke models (**Table 1**). More studies have used BM-MSCs than AD-MSCs or UC-MSCs.

BM-MSC-derived exosomes/EVs are known to promote neural plasticity and neurogenesis, as well as angiogenesis (Xin et al., 2013a; Doeppner et al., 2015; Deng et al., 2017; Dabrowska et al., 2019; Han et al., 2020). Most studies that showed effects of BM-MSC-derived exosomes/EVs used rat or mouse models of stroke. Go et al. (2020) used aged Rhesus monkeys and reported that EVs derived from BM-MSCs can improve motor function and reduce microglial mediated neuroinflammation in monkeys with cortical injury. Thus, exosomes/EVs derived from BM-MSCs are expected to exert therapeutic effects on aged human with brain damage.

In addition to these reports, exosomes/EVs released from AD-MSCs are known to reduce brain infarction and restore white matter integrity (Chen et al., 2016; Otero-Ortega et al., 2017). Although exosomes/EVs derived from cultured AD-MSCs using conventional methods are effective against ischemic lesions, Lee et al. (2016) demonstrated that microvesicles secreted from AD-MSCs cultured with brain extract exhibit greater potency for improving neurological functions than microvesicles secreted from AD-MSCs cultured without brain extract.

Besides AD-MSCs, exosomes secreted from human umbilical cord blood derived MSCs have been shown to exert beneficial effects in reducing infarct size by intravenous injection (Nalamolu et al., 2019). Exosomes derived from human UC-MSCs with overexpression of C-C chemokine receptor 2 are also effective for post-stroke cognitive impairment by promoting M2 microglia/macrophage polarization (Yang et al., 2020). In addition to UC-MSCs, small EVs secreted from human induced pluripotent stem cell (iPSC)-derived MSCs have been shown to inhibit abnormal autophagy and promote angiogenesis in an ischemic stroke model (Xia et al., 2020).

In the last few years, a large number of exosomal miRNAs that improve ischemia-induced brain damage have been identified (**Table 1**). Xin et al. (2013b) demonstrate that administration of miR-133b-overexpressing BM-MSCs promotes functional recovery via exosomal transfer into neurons and astrocytes. They also reported that miR-17-92 cluster-enriched exosomes, derived from BM-MSCs, can enhance functional recovery from stroke by promoting oligodendrogenesis, neurogenesis and neuronal remodeling (Xin et al., 2017).

Neurogenesis is known to be induced by miR-124, miR-126 and miR-184. In a mouse model of photothrombosis, miR-124-loaded exosomes derived from BM-MSCs is suggested to induce cortical neuronal progenitors to differentiate into the neuronal lineage (Yang et al., 2017). Exosomal miR-126 derived from AD stem cells and miR-184 derived from BM-MSCs can also promote functional recovery by enhancing neurogenesis in rat models of stroke (Geng et al., 2019; Moon et al., 2019)

Anti-inflammatory and immunomodulatory effects of MSC-derived exosomes are exerted by miR-30d, miR-126 and miR-138. Jiang et al. (2018) demonstrated that exosomal miR-30d derived from AD stem cells can decrease the cerebral injury by suppressing autophagy and promoting M2 microglia polarization. Exosomal miR-126 derived from AD stem cells acts to inhibit microglial activation and inflammatory reactions in a rat stroke model (Geng et al., 2019). In addition, exosomal miR-138 derived from BM-MSCs is known to ameliorate neurological impairments by inhibiting the inflammatory responses of astrocytes (Deng et al., 2019).

Angiogenic effects of MSC-derived exosomes are exerted by miR-29b, miR-132 and miR-210 in stroke models. Exosomal miR-29b derived from BM-MSCs can ameliorate ischemic brain injury by enhancing angiogenesis and inhibiting neuronal apoptosis (Hou et al., 2020). Exosomal miR-132 derived from BM-MSCs can protect brain injury by reducing vascular oxidative production and inhibiting blood-brain barrier dysfunction (Pan et al., 2020). In addition, Moon et al. (2019) demonstrate that miR-210 contained in EVs derived from BM-MSCs was essential for angiogenesis in a rat stroke model.

Effect of Exosomes/Extracellular Vesicles and Exosomal MicroRNAs Derived from Mesenchymal Stem Cells on Models of Subarachnoid and Intracerebral Hemorrhage

Exosomes/EVs secreted from BM-MSCs and AD-MSCs have been shown to have an effect on neuronal recovery in models of subarachnoid and intracerebral hemorrhage (**Table 2**). Exosomes derived from AD-MSCs are known to restore the integrity of white matter in a rat model of intracerebral hemorrhage by intravenous injection (Otero-Ortega et al., 2018). Zhang et al. (2018) found that miR-21 overexpressing BM-MSCs can promote the neurological functions via exosomal transfer into neurons in a rat model of intracerebral hemorrhage.

In SAH models, exosomal miR-21 and miR-193b derived from BM-MSCs are known to ameliorate the neurological impairments. Gao et al. (2020) reported that transfer of miR-21 from BM-MSCs to neurons protected neuronal apoptosis and improved cognitive function in a rat model of SAH. In addition, miR-193b-loaded exosomes derived from BM-MSCs were found to attenuate neuronal inflammation by systemic injection in a mouse model of SAH (Lai et al., 2020). In addition, miR-193b has an effect to decrease the edema and blood-brain barrier injury in damaged brain (Lai et al., 2020).

Effect of Exosomes/Extracellular Vesicles and Exosomal MicroRNAs Derived from Mesenchymal Stem Cells on Models of Traumatic Brain Injury

Exosomes/EVs secreted from BM-MSCs are known to improve the neuronal dysfunction in TBI models (**Table 3**). Although TBI is a major cause of mortality and long-term disability,

Table 1 | **Various application of stem cell-derived exosomes/EVs in models of stroke**

Study	MSC (source)	Vesicle type (administration)	miRNA (target gene)	Function	*In vivo* models
Xin et al. (2013a)	BM-MSCs (rat)	Exosomes (iv)	–	Neuroprotection/neurogenesis/ angiogenesis/neurological recovery	Rat model of stroke
Doeppner et al. (2015)	BM-MSCs (human)	EVs (iv)	–	Neuroprotection/neurogenesis/ immunomodulation/angiogenesis/ neurological recovery	Mouse model of stroke
Chen et al. (2016)	AD-MSCs (mini-pig)	Exosomes (iv)	–	Neuroprotection/anti-inflammation/ immunomodulation/angiogenesis/ neurological recovery	Rat model of acute ischemic stroke
Lee et al. (2016)	BE treated AD-MSCs (human)	MVs (ia)	–	Neuroprotection/neurogenesis/anti-inflammation/angiogenesis/neurological recovery	Rat model of stroke
Deng et al. (2017)	BM-MSCs (mouse)	EVs (icv)	–	Neuroprotection/anti-inflammation/ neurological recovery	Mouse model of transient global ischemia
Otero-Orteg et al. (2017)	AD-MSC (rat)	EVs (iv)	–	Neuroprotection/neurological recovery/ restore the white matter integrity	Rat model of subcortical stroke
Dabrowska et al. (2019)	BM-MSCs (human)	EVs (ia)	–	Neuroprotection/anti-inflammation/ immunomodulation	Rat model of focal brain injury
Nalamolu et al. (2019)	UCB-MSCs (human)	Exosomes (iv)	–	Neuroprotection	Rat model of stroke
Go et al. (2020)	BM-MSCs (monkey)	EVs (iv)	–	Anti-inflammation/immunomodulation/ neurological recovery	Aged rhesus monkey model of cortical injury
Han et al. (2020)	BM-MSCs (rat)	EVs (iv)	–	Neuroprotection/anti-inflammation/ neurological recovery	Rat model of cerebral ischemia/reperfusion injury
Xia et al. (2020)	iPSC-derived MSC (human)	small EVs (iv)	–	Neuroprotection/angiogenesis/ inhibiting autophagy/neurological recovery	Rat model of stroke
Yang et al. (2020)	CCR2 overexpressing UC-MSCs (human)	Exosomes (iv)	–	Neuroprotection/anti-inflammation/ immunomodulation/neurological recovery	Rat model of post-stroke cognitive impairment
Xin et al. (2013b)	miR-133b overexpressing BM-MSCs (rat) (iv)	Exosomes	miR-133b (RhoA)	Neuroprotection/neurological recovery	Rat model of stroke
Xin et al. (2017)	miR-17-92 overexpressing BM-MSCs (rat)	Exosomes (iv)	miR-17-92 (PTEN)	Neuroprotection/neurogenesis/ neurological recovery	Rat model of stroke
Yang et al. (2017)	BM-MSCs (mouse)	miR-124 loading RVG-exosomes (iv)	miR-124 (Gil3/Stat3)	Neurogenesis	Mouse model of photothrombosis
Jiang et al. (2018)	miR-30d overexpressing ADSCs (rat)	Exosomes (iv)	miR-30d (Beclin/ Atg5)	Neuroprotection/anti-inflammation/ immunomodulation/suppressing autophagy/neurological recovery	Rat model of acute ischemic stroke
Deng et al. (2019)	miR-138 overexpressing BM-MSCs (mouse)	Exosomes	miR-138 (LCN2)	Neuroprotection/anti-inflammation/ inhibit inflammatory responses of astrocytes	Mouse model of stroke
Geng et al. (2019)	miR-126 overexpressing ADSCs (rat)	Exosomes (iv)	miR-126	Neuroprotection/neurogenesis/ immunomodulation/angiogenesis/ neurological recovery	Rat model of stroke
Moon et al. (2019)	BM-MSCs (rat)	EVs (iv)	miR-184 (Numbl) miR-210 (EFNA3)	Neuroprotection/neurogenesis/ angiogenesis/neurological recovery	Rat model of stroke
Hou et al. (2020)	miR-29b overexpressing BM-MSCs (rat)	Exosomes (icv)	miR-29b (PTEN)	Neuroprotection/angiogenesis	Rat model of stroke
Pan et al. (2020)	miR-132 overexpressing BM-MSCs (mouse)	Exosomes (iv)	miR-132 (RASA1)	Inhibiting cerebral vascular ROS/reducing BBB dysfunction/neuroprotection	Mouse model of stroke

AD: Adipose derived; ADSCs: adipose-derived stem cells; BBB: blood-brain barrier; BE: brain-extract; BM: bone marrow; CCR2: C-C chemokine receptor type 2; EVs: extracellular vesicles; ia: intra-arterial injection; icv: intracerebroventricular injection; iPSC: induced pluripotent stem cell; iv: intravenous injection; MSCs: mesenchymal stem cells; MVs: microvesicles; ROS: reactive oxygen species; RVG: rabies virus glycoprotein; UC: umbilical cord; UCB: umbilical cord blood.

exosomes/EVs derived from BM-MSCs have an effect in improving sensorimotor function and cognitive impairment in TBI models by regulating angiogenesis, neurogenesis and neuroinflammation (Zhang et al., 2015; Kim et al., 2016; Ni et al., 2019). Rodent models are usually used in experiments on TBI. However, Williams et al. found that neurological function in a swine model of TBI combined with hemorrhagic shock was recovered by administration of exosomes derived from BM-MSCs (Williams et al., 2019). In addition, Xu et al. (2020) reported that exosomal miR-216a derived from BM-MSCs can inhibit TBI-induced neuronal apoptosis.

For the treatment of TBI, the proper dose of BM-MSC-derived exosomes and the timing of treatment have been investigated by Zhang et al. (2020). They found that intravenous injection of 100 μg of exosomes in TBI rats resulted in better neurological function than other groups treated with 50 μg or 200 μg of exosomes (Zhang et al., 2020). In addition, they found that rats receiving exosome injection at 1 day after TBI showed greater functional improvement, compared to other groups that received the exosome injection at 4 or 7 days after TBI (Zhang et al., 2020). Such results seem to be useful for clinical application. They also reported that exosomes derived from BM-MSCs cultured under 3-dimensional conditions showed greater effectiveness for the damage from TBI, compared to those from BM-MSCs cultured under 2-dimensional conditions (Zhang et al., 2017). Thus, not only the dose or timing, but also the culture condition of BM-MSCs seems important for therapy using exosomes.

Table 2 | **Various application of stem cell-derived exosomes/EVs in models of subarachnoid and intracerebral hemorrhage**

Study	MSC (source)	Vesicle type (administration)	miRNA (target gene)	Function	*In vivo* models
Otero-Ortega et al. (2018)	AD-MSCs (rat)	Exosomes (iv)	–	Restore the white matter integrity/ neuroprotection/neurological recovery	Rat model of ICH
Zhang et al. (2018)	miR-21 overexpressing BM-MSCs (rat) (intracerebral injection)	Exosomes	miR-21 (TRPM7)	Neuroprotection/anti-inflammation/ neurological recovery	Rat model of ICH
Gao et al. (2020)	BM-MSCs (rat)	EVs (iv)	miR-21 (PTEN)	Neuroprotection/neurological recovery	Rat model of SAH
Lai et al. (2020)	BM-MSCs (mouse)	miR-193b loading RVG-exosomes (iv)	miR-193b (HDAC3)	Neuroprotection/anti-inflammation/ neurological recovery	Mouse model of SAH

AD: Adipose derived; BM: bone marrow; EVs: extracellular vesicles; ICH: intracerebral hemorrhage; iv: intravenous injection; MSCs: mesenchymal stem cells; RVG: rabies virus glycoprotein; SAH: subarachnoid hemorrhage.

Table 3 | **Various application of stem cell-derived exosomes/EVs in models of traumatic brain injury**

Study	MSC (source)	Vesicle type (administration)	miRNA (target gene)	Function	*In vivo* models
Zhang et al. (2015)	BM-MSCs (rat)	Exosomes (iv)	–	Neuroprotection/neurogenesis/ angiogenesis/neurological recovery	Rat model of TBI
Kim et al. (2016)	BM-MSCs (human)	EVs (iv)	–	Anti-inflammation/neurological recovery	Mouse model of TBI
Zhang et al. (2017)	BM-MSCs cultured under 3D conditions (human)	Exosomes (iv)	–	Neurogenesis/anti-inflammation/ angiogenesis/neurological recovery	Rat model of TBI
Ni et al. (2019)	BM-MSCs (rat)	Exosomes (retro-orbital injection)	–	Neuroprotection/anti-inflammation/ immunomodulation/neurological recovery	Mouse model of TBI
Williams et al. (2019)	BM-MSCs (human)	Exosomes (iv)	–	Neurological recovery	Swine model of TBI and hemorrhagic shock
Zhang et al. (2020)	BM-MSCs; (human)	Exosomes (iv)	–	Neurogenesis/anti-inflammation/ angiogenesis/neurological recovery	Rat model of TBI
Xu et al. (2020)	BDNF treated BM-MSCs (rat)	Exosomes (iv)	miR-216a (HMGB1)	Neuroprotection/anti-inflammation/ neurogenesis/neurological recovery	Rat model of TBI

BDNF: Brain-derived neurotrophic factor; BM: bone marrow; EVs: extracellular vesicles; iv: intravenous injection; MSCs: mesenchymal stem cells; TBI: traumatic brain injury.

Effect of Exosomes/Extracellular Vesicles and Exosomal MicroRNAs Derived from Mesenchymal Stem Cells on Models of Cognitive Impairment, Including Alzheimer's Disease and Diabetes

Exosomes/EVs secreted from BM-MSCs are known to improve the function of learning and memory in models of cognitive impairment (**Table 4**). Alzheimer's disease is the most common cause of dementia, and neurodegeneration is thought to be induced by an accumulation of amyloid-β (Aβ) plaques and tau protein aggregates (Querfurth and LaFerla, 2010). Intracerebral injection of MSC-derived exosomes has recently been shown to promote neurogenesis and improve cognitive function in an Alzheimer's disease mouse model that received administration of Aβ to the dentate gyrus (Reza-Zaldivar et al., 2019). In addition, Elia et al. (2019) reported that intracerebral injection of BM-MSC-derived EVs can reduce the Aβ burden in APP/PS1 mice at 3–5 months of age, as a model of early-stage Alzheimer's disease. They suggested that the neprilysin contained in exosomes might degrade Aβ plaques (Elia et al., 2019). Cui et al. (2019) demonstrated that intravenously injected BM-MSC-derived exosomes, which were tagged with central nervous system-specific rabies viral glycoprotein peptide, showed therapeutic effects in improving cognitive function and reducing cytokine levels, when injected into APP/PS1 mice at 7–10 months old. In addition, intravenous injection of UC-MSC-derived exosomes improved cognitive dysfunctions by reducing Aβ plaques and modulating microglial activation, when injected into APP/PS1 mice at 7–8 months old (Ding et al., 2018). However, modifications such as rabies viral glycoprotein peptide tagging seems necessary for the effective delivery of exosomes to the central nervous system when intravenous injection is considered.

Exosomal miR21, miR-29b and miR-146a derived from BM-MSCs act to improve cognitive function in Alzheimer's disease models (Cui et al., 2018; Jahangard et al., 2020; Nakano et al., 2020). Cui et al. (2018) reported that exosomal miR-21 derived from hypoxia-preconditioned BM-MSCs can ameliorate cognitive declines by inhibiting synaptic dysfunction and inflammatory responses, when those exosomes were injected intravenously to APP/PS1 mice at 7–10 months old. In addition, exosomes derived from BM-MSCs transfected with miR-29b have been shown to improve Aβ-induced cognitive impairment in a rat Alzheimer's disease model injected with Aβ in the CA1 region (Jahangard et al., 2020). In our own recent study, intracerebroventricular injection of BM-MSCs was found to improve cognitive impairment in APP/PS1 mice of 13 months old (Nakano et al., 2020). Since the increased expression of miR-146a has been observed in the brain of APP/PS1 mice treated with BM-MSCs, exosomal transfer of miR-146a is suggested to ameliorate astrocytic inflammation in the brain of APP/PS1 mice. We also demonstrated that exosomal transfer of miR-146a reduced the inflammatory state of cultured astrocytes *in vitro* (Nakano et al., 2020).

In addition to Alzheimer's disease models, our group showed that exosomes from BM-MSCs improved the diabetes-induced cognitive impairment in streptozotocin-injected mice by reducing astroglial inflammation (Nakano et al., 2016). Exosomal miR-146a derived from BM-MSCs has also been suggested to improve diabetes-induced cognitive impairment by reducing astroglial inflammation in a streptozotocin-injected rat model (Kubota et al., 2018).

Table 4 | **Various application of stem cell-derived exosomes/EVs in models of cognitive impairment**

Study	MSC (source)	Vesicle type (administration)	miRNA (target gene)	Function	*In vivo* models
Nakano et al. (2016)	BM-MSCs (rat)	Exosomes (icv)	–	Neuroprotection/anti-inflammation/ immunomodulation/improve cognitive function	Mouse model of diabetes-induced cognitive impairment
Ding et al. (2018)	UC-MSCs (human)	Exosomes (iv)	–	Reduce Aβ plaque burden/ immunomodulation/anti-inflammation/ improve cognitive function	Mouse model of AD (APP/PS1)
Cui et al. (2019)	BM-MSCs (mouse)	RVG-modified Exosomes (iv)	–	Reduce Aβ plaque burden/anti-inflammation/ improve cognitive function	Mouse model of AD (APP/PS1)
Elia et al. (2019)	BM-MSCs (mouse)	EVs (into neocortex)	–	Neuroprotection/reduce Aβ plaque burden	Mouse model of AD (APP/PS1)
Reza-Zaldivar et al. (2019)	MSC	Exosomes (into DG)	–	Neurogenesis/improve cognitive function	Mouse model of AD (Aβ injected model)
Kubota et al. (2018)	BM-MSCs (rat) (iv)	Exosomes	miR-146a (IRAK1)	Neuroprotection/anti-inflammation/improve cognitive function	Mouse model of diabetes-induced cognitive impairment
Cui et al. (2018)	Hypoxia-preconditioned BM-MSCs (mouse)	Exosomes (iv)	miR-21 (STAT3/ NF-κB)	Neuroprotection/anti-inflammation/reduce Aβ plaque burden/improve cognitive function	Mouse model of AD (APP/PS1)
Jahangard et al. (2020)	miR-29b overexpressing BM-MSCs (rat)	Exosomes (into CA1)	miR-29b (NAV3/ BIM)	Improve cognitive function	Rat model of AD (Aβ injected model)
Nakano et al. (2020)	BM-MSCs (rat) (icv)	Exosomes	miR-146a (TRAF6)	Neuroprotection/anti-inflammation/ immunomodulation/improve cognitive function	Mouse model of AD (APP/PS1)

AD: Alzheimer's disease; Aβ: amyloid β; BM: bone marrow; CA1: cornu ammonis 1; DG: dentate gyrus; EVs: extracellular vesicles; icv: intracerebroventricular injection; iv: intravenous injection; MSCs: mesenchymal stem cells; RVG: rabies virus glycoprotein; UC: umbilical cord.

Effect of Exosomes/Extracellular Vesicles Derived from Mesenchymal Stem Cells on Other Models of Neurological Disorder

Exosomes/EVs derived from MSCs are known to promote neurological functions in other models, including perinatal brain injury, multiple sclerosis, Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), autism spectrum disorders (ASD), Machado-Joseph disease (MJD), status epilepticus (SE) and infection-induced brain damage (**Table 5**).

Exosomes/EVs derived from BM-MSCs and Wharton's jelly-derived (WJ)-MSCs have been shown to improve neurological inflammation in models of perinatal brain injury (Ophelders et al., 2016; Drommelschmidt et al., 2017; Sisa et al., 2019; Thomi et al., 2019a, b). BM-MSC-derived EVs can reduce glial activation, cell apoptosis and tissue volume loss in rodent models of perinatal brain injury induced by hypoxia-ischemia or lipopolysaccharide injection (Drommelschmidt et al., 2017; Sisa et al., 2019). BM-MSC-derived EVs have been shown to reduce seizures in a sheep model of fetal brain injury with hypoxia-ischemia insult by preventing hypomyelination (Ophelders et al., 2016). Since such a sheep model is similar to the clinical condition of human preterm brain with hypoxia-ischemia injury, exosomal treatment can be expected to prove effective in humans. Besides BM-MSCs, WJ-MSC-derived exosomes also contribute to functional recovery in rat models of prenatal brain injury (Thomi et al., 2019a, b). WJ-MSC-derived exosomes are known to rescue normal myelination, inhibit cell death of oligodendrocytes as well as neurons, and reduce microglia-mediated neuroinflammation (Thomi et al., 2019a, b).

Exosomes/EVs derived from placenta-derived MSCs, BM-MSCs and AD-MSCs have been shown to improve motor deficits in multiple sclerosis models (Laso-García et al., 2018; Clark et al., 2019; Riazifar et al., 2019). Multiple sclerosis is the most common autoimmune demyelinating disease of the central nervous system (Ransohoff et al., 2015). Clark et al. (2019) reported that EVs secreted from placenta-derived MSCs improve motor function by reducing DNA damage to oligodendrocytes and increasing myelination in the spinal cord in experimental autoimmune encephalomyelitis mice. Exosomes derived from BM-MSCs stimulated by IFN-γ have been shown to reduce demyelination as well as neuroinflammation, and to increase the number of regulatory T cells in the spinal cord of experimental autoimmune encephalomyelitis mice (Riazifar et al., 2019). Furthermore, EVs derived from AD-MSCs can improve motor functions by decreasing brain atrophy, promoting remyelination and regulating inflammatory state in the spinal cord of a mouse model of progressive multiple sclerosis (Laso-García et al., 2018).

Exosomes derived from MSCs are shown to improve neurological functions in models of PD and ALS (Bonafede et al., 2020; Chen et al., 2020a). PD is a common progressive neurodegenerative disease that leads to motor and cognitive dysfunctions (Poewe et al., 2017). Chen et al. (2020a) reported that exosomes derived from UC-MSCs ameliorated apomorphine-induced asymmetric rotation by reducing the loss of dopaminergic neurons in the substantia nigra and increasing levels of dopamine in the striatum. ALS is a neurodegenerative disease involving progressive degeneration of motor neurons, but no effective pharmacotherapies have so far been identified (Robberecht and Philips, 2013). Exosomes derived from AD stem cells have recently been shown to improve motor performance by protecting lumbar motor neurons and decreasing glial activation in a mouse model of ALS (Bonafede et al., 2020).

In addition to PD and ALS, exosomes derived from MSCs are shown to improve neurological behaviors in a model of MJD and ASD. MJD is the most common autosomal-dominant hereditary ataxia, but effective treatments remain lacking (Klockgether et al., 2019). You et al. (2020) reported that exosomes isolated from iPSC-derived MSCs can improve motor functions in a mouse model of MJD by attenuating losses of Purkinje cells and cerebellar myelin. ASD is a neurodevelopmental disorder characterized by deficits in social interactions, increased repetitive behaviors and cognitive inflexibility (Lord et al., 2020). Perets et al. (2018) demonstrated that intranasal injection of exosomes derived from BM-MSCs can increase social interaction and reduce repetitive behavior in a model of ASD.

Exosomes derived from BM-MSCs and WJ-MSCs are known to

Table 5 | **Various application of stem cell-derived exosomes/EVs in models of other neurological disorders**

Study	MSC (source)	Vesicle type (administration)	miRNA (target gene)	Function	*In vivo* models
Ophelders et al. (2016)	BM-MSCs (human)	EVs (iv)	–	Reduce white matter injury/ neuroprotection/neurological recovery	Ovine model of fetal brain injury induced by HI insult
Drommelschmidt et al. (2017)	BM-MSCs (human)	EVs (ip)	–	Neuroprotection/anti-inflammation/ immunomodulation/neurological recovery	Rat model of preterm brain injury induced by LPS injection
Sisa et al. (2019)	BM-MSCs (human)	EVs (in)	–	Neuroprotection/immunomodulation/ neurological recovery	Mouse model of prinatal brain injury induced by HI insult
Thomi et al. (2019a)	WJ-MSCs (human)	Exosomes (in)	–	Anti-inflammation/immunomodulation	Rat model of prinatal brain injury induced by HI and LPS insult
Thomi et al. (2019b)	WJ-MSCs (human)	Exosomes (in)	–	Prevent gray and white matter alterations/ neuroprotection/neurological recovery	Rat model of prinatal brain injury induced by HI and LPS insult
Laso-Garcia et al. (2018)	AD-MSCs (human)	EVs (iv)	–	Remyelination/anti-inflammation/ immunomodulation/neurological recovery	Mouse model of progressive MS
Clark et al. (2019)	Placenta-derived MSCs (human)	EVs (iv)	–	Remyelination/neurological recovery	Mouse model of MS
Riazifar et al. (2019)	IFN-γ activated BM-MSCs (human)	Exosomes (iv)	–	Remyelination/anti-inflammation/ immunomodulation/neurological recovery	Mouse model of MS
Chen et al. (2020a)	UC-MSCs (human)	Exosomes (iv)	–	Reduce dopaminergic neuron loss/ neurological recovery	Rat model of PD
Bonafede et al. (2020)	ASCs (mouse)	Exosomes (iv or in)	–	Neuroprotection/anti-inflammation/ neurological recovery	Mouse model of ALS
You et al. (2020)	iPSC-derived MSCs (human)	Exosomes (iv)	–	Attenuate the loss of Purkinje cells anti-inflammation/neurological recovery	Mouse model of MJD
Perets et al. (2018)	BM-MSCs (human)	Exosomes (in)	–	Reduce autistic-like behaviors	Mouse model of ASD
Long et al. (2017)	BM-MSCs (human)	Exosomes (in)	–	Anti-inflammation/neurogenesis/ neurological recovery	Mouse model of SE
Xian et al. (2019)	WJ-MSCs (human)	Exosomes (icv)	–	Attenuate reactive astrogliosis/ neurological recovery	Mouse model of SE
Chang et al. (2019)	AD-MSCs (rat)	Exosomes (iv)	–	Suppress the systemic inflammation/ protect the brain damage	Rat model of sepsis syndrome
Chen et al. (2019)	EP4 antagonist treated BM-MSCs (human)	EVs (intracardiac injection)	–	Neuroprotection/anti-inflammation/ immunomodulationneurological recovery	Mouse model of brain damage induced by DTA
Chen et al. (2020b)	EP4 antagonist treated BM-MSCs (human)	EVs (intracardiac injection)	–	CNP promotes neurogenesis/ neuritogenesis/neurological recovery	Mouse model of brain damage induced by DTA

AD: Adipose-derived; ALS: amyotrophic lateral sclerosis; ASCs: adipose-derived stem cells; ASD: autism spectrum disorders; BM: bone marrow; CNP: 2',3'-cyclic nucleotide 3'phosphodiesterase; DTA: diphtheria toxin A; EP4: prostaglandin E2 receptor 4; EVs: extracellular vesicles; HI: hypoxia-ischemia; icv: intracerebroventricular injection; IFN-γ: interferon-γ; in: intranasal injection; ip: intraperitoneal injection; iPSC: induced pluripotent stem cell; iv: intravenous injection; LPS: lipopolysaccharide; MJD: Machado-Joseph disease; MS: multiple sclerosis; MSCs: mesenchymal stem cells; PD: Parkinson's disease; SE: status epilepticus; UC: umbilical cord; WJ: Wharton' jelly.

ameliorate the neurological changes accompanying SE (Long et al., 2017; Xian et al., 2019). Long et al. (2017) demonstrated that BM-MSC-derived A1 exosomes, which exhibit high anti-inflammatory properties, could improve cognitive impairment by ameliorating neuroinflammation and preventing abnormal neurogenesis in mice with pilocarpine-induced SE. In addition to A1 exosomes, WJ-MSC-derived exosomes are also known to improve learning and memory impairments by reducing astrocytic inflammation in pilocarpine-induced SE mice (Xian et al., 2019)

The brain damage induced by septic syndrome or bacterial toxins can be ameliorated by exosomes/EVs derived from MSCs (Chang et al., 2019; Chen et al., 2019, 2020b). Chang et al. (2019) reported that AD-MSC-derived exosomes can down-regulate inflammatory reactions in both the circulation and brain, in a model of sepsis induced by cecum ligation and puncture. Exosomes/EVs derived from BM-MSCs treated with an antagonist of prostaglandin E2 receptor 4 are also known to ameliorate the brain damage induced by diphtheria toxin A (Chen et al., 2019, 2020b). Chen et al. (2020b) showed that exosomes/EVs derived from BM-MSCs treated with E2 receptor 4 antagonist contain higher levels of 2′,3′-cyclic nucleotide 3′-phosphodiesterase, compared to those derived from untreated BM-MSCs. Such exosomal 2′,3′-cyclic nucleotide 3′-phosphodiesterase contributes to improve hippocampal neurogenesis and cognitive impairment in a mouse model of brain damage induced by diphtheria toxin A insult (Chen et al., 2020b).

Conclusion and Perspectives

Unlike cell therapies, administration of exosomes/EVs derived from MSCs seem to carry no risks of adverse effects such as tumor formation, cellular rejection and thrombosis. In contrast to iPSCs and embryonic stem cells which show higher potential to transform into teratomas, MSCs have been shown to be less tumorigenic (Neri, 2019). However, it is still controversial because some reports have shown that MSCs might have a property to enhance tumor growth by immunosuppressive effects (Klopp et al., 2011). Many kinds of miRNAs that are important to reducing neuroinflammation have been identified, and several clinical trials of MSC-derived exosome therapy have been started for acute ischemic stroke (NCT03384433) and Alzheimer's disease (NCT04388982). Thus, various methods have been defined to isolate EVs from conditioned media, including ultracentrifugation, precipitation and immunoaffinity (Phan et al., 2018). However, confirming complete purification of exosomes/EVs and complete removal of non-EV contaminants like lipoprotein complexes remains difficult (Phan et al., 2018). Therefore, it seems to be difficult to guarantee the reproducibility of these studies using exosomes/EVs. Besides exosomal miRNAs, the injection of miRNA mimic oligonucleotide is also shown to improve the pathology of neurological diseases (Paul et al., 2020). For example, intracerebral injection of miR-7 mimic is reported to improve motor function and decrease lesion volume in rat stroke model (Kim et al., 2018). However the level of miR-7 in brain was shown to be decreased at 72 hours after injection. Half-lives of miRNAs that are not enclosed in EVs are short,

while miRNAs enclosed in EVs are less degraded (Coenen-Stass et al., 2019). Furthermore, MSC derived EVs contain not only miRNAs but also a lot of anti-inflammatory proteins (Qiu et al., 2019). Therefore, the injection of only miRNA mimic seems not to be suitable for the treatment of neurological diseases compared to the injection of MSC or MSC derived EVs.

In contrast to studies using MSC-derived EVs, a large number of clinical trials have used MSCs themselves. Over 950 registered MSC clinical trials are listed by the Food and Drug Administration, but only 188 phase 1 or 2 trials have been completed and ten studies have reached phase 3 (Pittenger et al., 2019). Thus, a large discrepancy seems to exist between human and animal studies, because a large number of papers have probed the efficacy of MSCs in various rodent models.

Some studies have suggested that MSC-derived exosomes/EVs exert more beneficial effects than MSCs themselves (Kim et al., 2016; Dabrowska et al., 2019). However, before jumping to this new treatment, clarifying why some clinical trials using MSCs did not go well might yield important insights. Clinical outcomes might be affected by the number of injected cells, route of injection, environment of culture or stage of disease. Identifying these problems and investigating further mechanisms of exosomal treatment will likely lead to promising new therapies aimed at overcoming neurological disorders.

Author contributions: *MN searched literatures and wrote the manuscript. MF corrected this manuscript. Both authors approved the final version of the manuscript.*
Conflicts of interest: *There are no conflicts of interest associated with this article.*
Financial support: *None.*

Plagiarism check: *Checked twice by iThenticate.*
Peer review: *Externally peer reviewed.*

Open peer reviewer: *Mónica Sanchez, Instituto Investigación Médica Mercedes y Martín Ferreyra, Argentina.*
Additional file: *Open peer review report 1.*

References

Bhaskaran M, Mohan M (2014) MicroRNAs: history, biogenesis, and their evolving role in animal development and disease. Vet Pathol 51:759-774.
Bonafede R, Turano E, Scambi I, Busato A, Bontempi P, Virla F, Schiaffino L, Marzola P, Bonetti B, Mariotti R (2020) ASC-exosomes ameliorate the disease progression in SOD1(G93A) murine model underlining their potential therapeutic use in human ALS. Int J Mol Sci 21:3651.
Chang CL, Chen HH, Chen KH, Chiang JY, Li YC, Lin HS, Sung PH, Yip HK (2019) Adipose-derived mesenchymal stem cell-derived exosomes markedly protected the brain against sepsis syndrome induced injury in rat. Am J Transl Res 11:3955-3971.
Chen HX, Liang FC, Gu P, Xu BL, Xu HJ, Wang WT, Hou JY, Xie DX, Chai XQ, An SJ (2020a) Exosomes derived from mesenchymal stem cells repair a Parkinson's disease model by inducing autophagy. Cell Death Dis 11:288.
Chen KH, Chen CH, Wallace CG, Yuen CM, Kao GS, Chen YL, Shao PL, Chen YL, Chai HT, Lin KC, Liu CF, Chang HW, Lee MS, Yip HK (2016) Intravenous administration of xenogenic adipose-derived mesenchymal stem cells (ADMSC) and ADMSC-derived exosomes markedly reduced brain infarct volume and preserved neurological function in rat after acute ischemic stroke. Oncotarget 7:74537-74556.
Chen SY, Lin MC, Tsai JS, He PL, Luo WT, Herschman H, Li HJ (2019) EP(4) Antagonist-elicited extracellular vesicles from mesenchymal stem cells rescue cognition/learning deficiencies by restoring brain cellular functions. Stem Cell Transl Med 8:707-723.
Chen SY, Lin MC, Tsai JS, He PL, Luo WT, Chiu IM, Herschman HR, Li HJ (2020b) Exosomal 2',3'-CNP from mesenchymal stem cells promotes hippocampus CA1 neurogenesis/neuritogenesis and contributes to rescue of cognition/learning deficiencies of damaged brain. Stem Cell Transl Med 9:499-517.
Clark K, Zhang S, Barthe S, Kumar P, Pivetti C, Kreutzberg N, Reed C, Wang Y, Paxton Z, Farmer D, Guo F, Wang A (2019) Placental mesenchymal stem cell-derived extracellular vesicles promote myelin regeneration in an animal model of multiple sclerosis. Cells 8:1497.
Coenen-Stass AML, Pauwels MJ, Hanson B, Martin Perez C, Conceição M, Wood MJA, Mäger I, Roberts TC (2019) Extracellular microRNAs exhibit sequence-dependent stability and cellular release kinetics. RNA Biol 16:696-706.
Cui GH, Guo HD, Li H, Zhai Y, Gong ZB, Wu J, Liu JS, Dong YR, Hou SX, Liu JR (2019) RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease. Immun Ageing 16:10.
Cui GH, Wu J, Mou FF, Xie WH, Wang FB, Wang QL, Fang J, Xu YW, Dong YR, Liu JR, Guo HD (2018) Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. FASEB J 32:654-668.
Dabrowska S, Andrzejewska A, Strzemecki D, Muraca M, Janowski M, Lukomska B (2019) Human bone marrow mesenchymal stem cell-derived extracellular vesicles attenuate neuroinflammation evoked by focal brain injury in rats. J Neuroinflammation 16:216.
Deng M, Xiao H, Zhang H, Peng H, Yuan H, Xu Y, Zhang G, Hu Z (2017) Mesenchymal stem cell-derived extracellular vesicles ameliorates hippocampal synaptic impairment after transient global ischemia. Front Cell Neurosci 11:205.
Deng Y, Chen D, Gao F, Lv H, Zhang G, Sun X, Liu L, Mo D, Ma N, Song L, Huo X, Yan T, Zhang J, Miao Z (2019) Exosomes derived from microRNA-138-5p-overexpressing bone marrow-derived mesenchymal stem cells confer neuroprotection to astrocytes following ischemic stroke via inhibition of LCN2. J Bio Eng 13:71.
Ding M, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, Wang Y, Lyu Y, Wang D, Xu L, Bi J, Yang H (2018) Exosomes isolated from human umbilical cord mesenchymal stem cells alleviate neuroinflammation and reduce amyloid-beta deposition by modulating microglial activation in Alzheimer's disease. Neurochem Res 43:2165-2177.
Doeppner TR, Herz J, Görgens A, Schlechter J, Ludwig AK, Radtke S, de Miroschedji K, Horn PA, Giebel B, Hermann DM (2015) Extracellular vesicles improve post-stroke neuroregeneration and prevent postischemic immunosuppression. Stem Cells Transl Med 4:1131-1143.
Drommelschmidt K, Serdar M, Bendix I, Herz J, Bertling F, Prager S, Keller M, Ludwig AK, Duhan V, Radtke S, de Miroschedji K, Horn PA, van de Looij Y, Giebel B, Felderhoff-Müser U (2017) Mesenchymal stem cell-derived extracellular vesicles ameliorate inflammation-induced preterm brain injury. Brain Behav Immun 60:220-232.
Elia CA, Tamborini M, Rasile M, Desiato G, Marchetti S, Swuec P, Mazzitelli S, Clemente F, Anselmo A, Matteoli M, Malosio ML, Coco S (2019) Intracerebral injection of extracellular vesicles from mesenchymal stem cells exerts reduced Aβ plaque burden in early stages of a preclinical model of Alzheimer's disease. Cells 8:1059.
Gao X, Xiong Y, Li Q, Han M, Shan D, Yang G, Zhang S, Xin D, Zhao R, Wang Z, Xue H, Li G (2020) Extracellular vesicle-mediated transfer of miR-21-5p from mesenchymal stromal cells to neurons alleviates early brain injury to improve cognitive function via the PTEN/Akt pathway after subarachnoid hemorrhage. Cell Death Dis 11:363.
Geng W, Tang H, Luo S, Lv Y, Liang D, Kang X, Hong W (2019) Exosomes from miRNA-126-modified ADSCs promotes functional recovery after stroke in rats by improving neurogenesis and suppressing microglia activation. Am J Transl Res 11:780-792.
Go V, Bowley BGE, Pessina MA, Zhang ZG, Chopp M, Finklestein SP, Rosene DL, Medalla M, Buller B, Moore TL (2020) Extracellular vesicles from mesenchymal stem cells reduce microglial-mediated neuroinflammation after cortical injury in aged Rhesus monkeys. GeroScience 42:1-17.
Han M, Cao Y, Xue H, Chu X, Li T, Xin D, Yuan L, Ke H, Li G, Wang Z (2020) Neuroprotective effect of mesenchymal stromal cell-derived extracellular vesicles against cerebral ischemia-reperfusion-induced neural functional injury: a pivotal role for AMPK and JAK2/STAT3/NF-κB signaling pathway modulation. Drug Des Devel Ther 14:2865-2876.
Heo JS, Choi Y, Kim HS, Kim HO (2016) Comparison of molecular profiles of human mesenchymal stem cells derived from bone marrow, umbilical cord blood, placenta and adipose tissue. Int J Mol Med 37:115-125.
Hou K, Li G, Zhao J, Xu B, Zhang Y, Yu J, Xu K (2020) Bone mesenchymal stem cell-derived exosomal microRNA-29b-3p prevents hypoxic-ischemic injury in rat brain by activating the PTEN-mediated Akt signaling pathway. J Neuroinflammation 17:46.
Jahangard Y, Monfared H, Moradi A, Zare M, Mirnajafi-Zadeh J, Mowla SJ (2020) Therapeutic effects of transplanted exosomes containing miR-29b to a rat model of Alzheimer's disease. Front Neurosci 14:564.
Jiang M, Wang H, Jin M, Yang X, Ji H, Jiang Y, Zhang H, Wu F, Wu G, Lai X, Cai L, Hu R, Xu L, Li L (2018) Exosomes from MiR-30d-5p-ADSCs reverse acute ischemic stroke-induced, autophagy-mediated brain injury by promoting M2 microglial/macrophage polarization. Cell Physiol Biochem 47:864-878.
Kim DK, Nishida H, An SY, Shetty AK, Bartosh TJ, Prockop DJ (2016) Chromatographically isolated CD63+CD81+ extracellular vesicles from mesenchymal stromal cells rescue cognitive impairments after TBI. Proc Natl Acad Sci U S A 113:170-175.
Kim T, Mehta SL, Morris-Blanco KC, Chokkalla AK, Chelluboina B, Lopez M, Sullivan R, Kim HT, Cook TD, Kim JY, Kim H, Kim C, Vemuganti R (2018) The microRNA miR-7a-5p ameliorates ischemic brain damage by repressing α-synuclein. Sci Signal 11:eaat4285.
Klockgether T, Mariotti C, Paulson HL (2019) Spinocerebellar ataxia. Nat Rev Dis Primers 5:24.
Klopp AH, Gupta A, Spaeth E, Andreeff M, Marini F, 3rd (2011) Concise review: Dissecting a discrepancy in the literature: do mesenchymal stem cells support or suppress tumor growth? Stem Cells 29:11-19.
Kubota K, Nakano M, Kobayashi E, Mizue Y, Chikenji T, Otani M, Nagaishi K, Fujimiya M (2018) An enriched environment prevents diabetes-induced cognitive impairment in rats by enhancing exosomal miR-146a secretion from endogenous bone marrow-derived mesenchymal stem cells. PLoS One 13:e0204252.

Lai CP, Tannous BA, Breakefield XO (2014) Noninvasive in vivo monitoring of extracellular vesicles. Methods Mol Biol 1098:249-258.
Lai N, Wu D, Liang T, Pan P, Yuan G, Li X, Li H, Shen H, Wang Z, Chen G (2020) Systemic exosomal miR-193b-3p delivery attenuates neuroinflammation in early brain injury after subarachnoid hemorrhage in mice. J Neuroinflammation 17:74.
Laso-García F, Ramos-Cejudo J, Carrillo-Salinas FJ, Otero-Ortega L, Feliú A, Gómez-de Frutos M, Mecha M, Díez-Tejedor E, Guaza C, Gutiérrez-Fernández M (2018) Therapeutic potential of extracellular vesicles derived from human mesenchymal stem cells in a model of progressive multiple sclerosis. PloS One 13:e0202590.
Lee JY, Kim E, Choi SM, Kim DW, Kim KP, Lee I, Kim HS (2016) Microvesicles from brain-extract-treated mesenchymal stem cells improve neurological functions in a rat model of ischemic stroke. Sci Rep 6:33038.
Long Q, Upadhya D, Hattiangady B, Kim DK, An SY, Shuai B, Prockop DJ, Shetty AK (2017) Intranasal MSC-derived A1-exosomes ease inflammation, and prevent abnormal neurogenesis and memory dysfunction after status epilepticus. Proc Natl Acad Sci U S A 114:E3536-3545.
Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, Jones EJH, Jones RM, Pickles A, State MW, Taylor JL, Veenstra-VanderWeele J (2020) Autism spectrum disorder. Nat Rev Dis Primers 6:5.
Moon GJ, Sung JH, Kim DH, Kim EH, Cho YH, Son JP, Cha JM, Bang OY (2019) Application of Mesenchymal Stem Cell-Derived Extracellular Vesicles for Stroke: Biodistribution and MicroRNA Study. Transl Stroke Res 10:509-521.
Nakano M, Nagaishi K, Konari N, Saito Y, Chikenji T, Mizue Y, Fujimiya M (2016) Bone marrow-derived mesenchymal stem cells improve diabetes-induced cognitive impairment by exosome transfer into damaged neurons and astrocytes. Sci Rep 6:24805.
Nakano M, Kubota K, Kobayashi E, Chikenji TS, Saito Y, Konari N, Fujimiya M (2020) Bone marrow-derived mesenchymal stem cells improve cognitive impairment in an Alzheimer's disease model by increasing the expression of microRNA-146a in hippocampus. Sci Rep 10:10772.
Nalamolu KR, Venkatesh I, Mohandass A, Klopfenstein JD, Pinson DM, Wang DZ, Veeravalli KK (2019) Exosomes treatment mitigates ischemic brain damage but does not improve post-stroke neurological outcome. Cell Physiol Biochem 52:1280-1291.
Neri S (2019) Genetic stability of mesenchymal stromal cells for regenerative medicine applications: a fundamental biosafety aspect. Int J Mol Sci 20:2406.
Ni H, Yang S, Siaw-Debrah F, Hu J, Wu K, He Z, Yang J, Pan S, Lin X, Ye H, Xu Z, Wang F, Jin K, Zhuge Q, Huang L (2019) Exosomes derived from bone mesenchymal stem cells ameliorate early inflammatory responses following traumatic brain injury. Front Neurosci 13:14.
Nooshabadi VT, Mardpour S, Yousefi-Ahmadipour A, Allahverdi A, Izadpanah M, Daneshimehr F, Ai J, Banafshe HR, Ebrahimi-Barough S (2018) The extracellular vesicles-derived from mesenchymal stromal cells: A new therapeutic option in regenerative medicine. J Cell Biochem 119:8048-8073.
Ophelders DR, Wolfs TG, Jellema RK, Zwanenburg A, Andriessen P, Delhaas T, Ludwig AK, Radtke S, Peters V, Janssen L, Giebel B, Kramer BW (2016) Mesenchymal stromal cell-derived extracellular vesicles protect the fetal brain after hypoxia-ischemia. Stem Cells Transl Med 5:754-763.
Otero-Ortega L, Laso-García F, Gómez-de Frutos MD, Rodríguez-Frutos B, Pascual-Guerra J, Fuentes B, Díez-Tejedor E, Gutiérrez-Fernández M (2017) White matter repair after extracellular vesicles administration in an experimental animal model of subcortical stroke. Sci Rep 7:44433.
Otero-Ortega L, Gómez de Frutos MC, Laso-García F, Rodríguez-Frutos B, Medina-Gutiérrez E, López JA, Vázquez J, Díez-Tejedor E, Gutiérrez-Fernández M (2018) Exosomes promote restoration after an experimental animal model of intracerebral hemorrhage. J Cereb Blood Flow Metab 38:767-779.
Pan Q, Kuang X, Cai S, Wang X, Du D, Wang J, Wang Y, Chen Y, Bihl J, Chen Y, Zhao B, Ma X (2020) miR-132-3p priming enhances the effects of mesenchymal stromal cell-derived exosomes on ameliorating brain ischemic injury. Stem Cell Res Ther 11:260.
Paul S, Bravo Vázquez LA, Pérez Uribe S, Roxana Reyes-Pérez P, Sharma A (2020) Current status of microRNA-based therapeutic approaches in neurodegenerative disorders. Cells 9:1698.
Perets N, Hertz S, London M, Offen D (2018) Intranasal administration of exosomes derived from mesenchymal stem cells ameliorates autistic-like behaviors of BTBR mice. Mol Autism 9:57.
Phan J, Kumar P, Hao D, Gao K, Farmer D, Wang A (2018) Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy. J Extracell Vesicles 7:1522236.
Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI (2019) Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regen Med 4:22.
Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, Schrag AE, Lang AE (2017) Parkinson disease. Nat Rev Dis Primers 3:17013.
Qiu G, Zheng G, Ge M, Wang J, Huang R, Shu Q, Xu J (2019) Functional proteins of mesenchymal stem cell-derived extracellular vesicles. Stem Cell Res Ther 10:359.
Querfurth HW, LaFerla FM (2010) Alzheimer's disease. N Engl J Med 362:329-344.
Ransohoff RM, Hafler DA, Lucchinetti CF (2015) Multiple sclerosis-a quiet revolution. Nat Rev Neurol 11:134-142.
Reza-Zaldivar EE, Hernández-Sapiéns MA, Gutiérrez-Mercado YK, Sandoval-Ávila S, Gomez-Pinedo U, Márquez-Aguirre AL, Vázquez-Méndez E, Padilla-Camberos E, Canales-Aguirre AA (2019) Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regen Res 14:1626-1634.
Riazifar M, Mohammadi MR, Pone EJ, Yeri A, Lässer C, Segaliny AI, McIntyre LL, Shelke GV, Hutchins E, Hamamoto A, Calle EN, Crescitelli R, Liao W, Pham V, Yin Y, Jayaraman J, Lakey JRT, Walsh CM, Van Keuren-Jensen K, Lotvall J, et al. (2019) Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders. ACS Nano 13:6670-6688.
Robberecht W, Philips T (2013) The changing scene of amyotrophic lateral sclerosis. Nat Rev Neurosci 14:248-264.
Saeedi P, Halabian R, Imani Fooladi AA (2019) A revealing review of mesenchymal stem cells therapy, clinical perspectives and Modification strategies. Stem Cell Investig 6:34.
Sisa C, Kholia S, Naylor J, Herrera Sanchez MB, Bruno S, Deregibus MC, Camussi G, Inal JM, Lange S, Hristova M (2019) Mesenchymal stromal cell derived extracellular vesicles reduce hypoxia-ischaemia induced perinatal brain injury. Front Physiol 10:282.
Thomi G, Surbek D, Haesler V, Joerger-Messerli M, Schoeberlein A (2019a) Exosomes derived from umbilical cord mesenchymal stem cells reduce microglia-mediated neuroinflammation in perinatal brain injury. Stem Cell Res Ther 10:105.
Thomi G, Joerger-Messerli M, Haesler V, Muri L, Surbek D, Schoeberlein A (2019b) Intranasally administered exosomes from umbilical cord stem cells have preventive neuroprotective effects and contribute to functional recovery after perinatal brain injury. Cells 8:855.
Williams AM, Dennahy IS, Bhatti UF, Halaweish I, Xiong Y, Chang P, Nikolian VC, Chtraklin K, Brown J, Zhang Y, Zhang ZG, Chopp M, Buller B, Alam HB (2019) Mesenchymal stem cell-derived exosomes provide neuroprotection and improve long-term neurologic outcomes in a swine model of traumatic brain injury and hemorrhagic shock. J Neurotrauma 36:54-60.
Xia Y, Ling X, Hu G, Zhu Q, Zhang J, Li Q, Zhao B, Wang Y, Deng Z (2020) Small extracellular vesicles secreted by human iPSC-derived MSC enhance angiogenesis through inhibiting STAT3-dependent autophagy in ischemic stroke. Stem Cell Res Ther 11:313.
Xian P, Hei Y, Wang R, Wang T, Yang J, Li J, Di Z, Liu Z, Baskys A, Liu W, Wu S, Long Q (2019) Mesenchymal stem cell-derived exosomes as a nanotherapeutic agent for amelioration of inflammation-induced astrocyte alterations in mice. Theranostics 9:5956-5975.
Xin H, Li Y, Cui Y, Yang JJ, Zhang ZG, Chopp M (2013a) Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. J Cereb Blood Flow Metab 33:1711-1715.
Xin H, Li Y, Liu Z, Wang X, Shang X, Cui Y, Zhang ZG, Chopp M (2013b) MiR-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells in rats via transfer of exosome-enriched extracellular particles. Stem Cells 31:2737-2746.
Xin H, Katakowski M, Wang F, Qian JY, Liu XS, Ali MM, Buller B, Zhang ZG, Chopp M (2017) MicroRNA cluster miR-17-92 cluster in exosomes enhance neuroplasticity and functional recovery after stroke in rats. Stroke 48:747-753.
Xu H, Jia Z, Ma K, Zhang J, Dai C, Yao Z, Deng W, Su J, Wang R, Chen X (2020) Protective effect of BMSCs-derived exosomes mediated by BDNF on TBI via miR-216a-5p. Med Sci Monit 26:e920855.
Yang HC, Zhang M, Wu R, Zheng HQ, Zhang LY, Luo J, Li LL, Hu XQ (2020) C-C chemokine receptor type 2-overexpressing exosomes alleviated experimental post-stroke cognitive impairment by enhancing microglia/macrophage M2 polarization. World J Stem Cells 12:152-167.
Yang J, Zhang X, Chen X, Wang L, Yang G (2017) Exosome mediated delivery of miR-124 promotes neurogenesis after ischemia. Mol Ther Nucleic Acids 7:278-287.
You HJ, Fang SB, Wu TT, Zhang H, Feng YK, Li XJ, Yang HH, Li G, Li XH, Wu C, Fu QL, Pei Z (2020) Mesenchymal stem cell-derived exosomes improve motor function and attenuate neuropathology in a mouse model of Machado-Joseph disease. Stem Cell Res Ther 11:222.
Zhang H, Wang Y, Lv Q, Gao J, Hu L, He Z (2018) MicroRNA-21 overexpression promotes the neuroprotective efficacy of mesenchymal stem cells for treatment of intracerebral hemorrhage. Front Neurol 9:931.
Zhang Y, Zhang Y, Chopp M, Zhang ZG, Mahmood A, Xiong Y (2020) Mesenchymal stem cell-derived exosomes improve functional recovery in rats after traumatic brain injury: a dose-response and therapeutic window study. Neurorehabil Neural Repair 34:616-626.
Zhang Y, Chopp M, Meng Y, Katakowski M, Xin H, Mahmood A, Xiong Y (2015) Effect of exosomes derived from multipluripotent mesenchymal stromal cells on functional recovery and neurovascular plasticity in rats after traumatic brain injury. J Neurosurg 122:856-867.
Zhang Y, Chopp M, Zhang ZG, Katakowski M, Xin H, Qu C, Ali M, Mahmood A, Xiong Y (2017) Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury. Neurochem Int 111:69-81.

P-Reviewer: Sanchez M; C-Editors: Zhao M, Liu WJ, Qiu Y; T-Editor: Jia Y