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Editorial Board Member of *World Journal of Stem Cells*, Radwa A Mehanna, MD, PhD, Professor, Physiology Department, Vice Executive Manager, Center of Excellence For Research in Regenerative Medicine and its Applications CERRMA, Faculty of Medicine, Alexandria University, Alexandria 21561, Egypt.
radwa.mehanna@alexmed.edu.eg

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MINIREVIEWS

Mesenchymal stem cells as a potential therapeutic tool to cure cognitive impairment caused by neuroinflammation

Maryna Skok

ORCID number: Maryna Skok 0000-0002-5816-605X.

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Maryna Skok, Department of Molecular Immunology, Palladin Institute of Biochemistry NAS of Ukraine, Kyiv 01054, Ukraine

Corresponding author: Maryna Skok, DSc, Academic Fellow, Professor, Senior Researcher, Department of Molecular Immunology, Palladin Institute of Biochemistry NAS of Ukraine, 9 Leontovicha str., Kyiv 01054, Ukraine. skok@biochem.kiev.ua

Abstract

An established contribution of neuroinflammation to multiple brain pathologies has raised the requirement for therapeutic strategies to overcome it in order to prevent age- and disease-dependent cognitive decline. Mesenchymal stem cells (MSCs) produce multiple growth and neurotrophic factors and seem to evade immune rejection due to low expression of major histocompatibility complex class I molecules. Therefore, MSCs are widely used in experiments and clinical trials of regenerative medicine. This review summarizes recent data concerning the optimization of MSC use for therapeutic purposes with the emphasis on the achievements of the last 2 years. Specific attention is paid to extracellular vesicles secreted by MSCs and to the role of α7 nicotinic acetylcholine receptors. The reviewed data demonstrate that MSCs have a significant therapeutic potential in treating neuroinflammation-related cognitive disfunctions including age-related neurodegenerative diseases. The novel data demonstrate that maximal therapeutic effect is being achieved when MSCs penetrate the brain and produce their stimulating factors *in situ*. Consequently, therapeutic application using MSCs should include measures to facilitate their homing to the brain, support the survival in the brain microenvironment, and stimulate the production of neurotrophic and anti-inflammatory factors. These measures include but are not limited to genetic modification of MSCs and pre-conditioning before transplantation.

Key Words: Mesenchymal stem cells; Neuroinflammation; Cognition; α7 Nicotinic acetylcholine receptor; Extracellular vesicles; Alzheimer disease

Core Tip: Mesenchymal stem cells (MSCs) have a significant therapeutic potential in

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treating neuroinflammation-related cognitive disfunctions including age-related neurodegenerative diseases. The review summarizes recent data concerning optimization of MSC use for therapeutic purposes with the emphasis on the achievements of the last 2 years. Specific attention is paid to extracellular vesicles secreted by MSCs and to the role of α7 nicotinic acetylcholine receptors. The main conclusion is that therapeutic application of MSCs should include measures to facilitate their homing to the brain, support the survival in the brain microenvironment and stimulate the production of neurotrophic and anti-inflammatory factors.

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INTRODUCTION

Neuroinflammation is an inflammatory response within the central nervous system: The brain or spinal cord. It is mediated by pro-inflammatory cytokines [interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α], chemokines (CCL2, CCL5, CXCL1), reactive oxygen species and secondary messengers (NO and prostaglandins) produced by glia (microglia and astrocytes), endothelial cells, and peripherally derived immune cells[1,2]. Neuroinflammation is a physiological response to infection, traumatic brain injury, toxic metabolites, or autoimmunity and, if appropriately controlled, is beneficial to the host organism. It induces symptoms including fever, weakness, and headache, and supports the recovery mechanisms. Physiological levels of IL-1β, presumably released from neurons, function as a neuromodulator to promote memory acquisition and retention. In contrast, high levels of IL-1β produced by astrocytes or resident microglial cells lead to failure of memory acquisition or recall[3]. IL-6 is often regarded as a neurotrophic factor[4,5], which contributes to the normal function of the brain, including learning and memory[6], while elevated IL-6 promotes astrogliosis and microgliosis, which are signs of neuroinflammation[7]. Chronic, uncontrolled inflammation is characterized by increased production of cytokines (IL-1β and TNF-α), reactive oxygen species, and other inflammatory mediators. Monocyte and macrophage recruitment to the brain causes anxiety and depression[2]. A low-level and chronic inflammatory response driven by IL-1β and IL-6 is caused by aging and leads to reduced neuronal plasticity and cognitive impairments. A special term "inflammaging" has been introduced to define a critical relation of inflammatory and aging processes[8]. A higher degree of chronic inflammation is greatly damaging to the nervous system and is characteristic of age-related neurodegenerative disorders like Alzheimer disease (AD) and Parkinson disease[9-11]. In experimental models, inducing neuroinflammation by injecting mice with bacterial lipopolysaccharide (LPS) results in impairment of episodic memory followed by accumulation of pathogenic fragments of amyloid-β in the brain, which is characteristic of the early form of AD [12]. Apart from the aging and neurodegenerative diseases, neuroinflammation accompanies numerous neurological disorders like migraine[13], neuropathic pain [14], stroke[15], and multiple sclerosis[16].

An established contribution of neuroinflammation to multiple brain pathologies has raised the requirement of therapeutic strategies to overcome it in order to prevent age- and disease-dependent cognitive decline. Traditional targets for neuroinflammation include purinergic receptors $P2X_4$ and $P2X_7$, kynurenine pathway metabolizing enzymes indole 2,3-dioxygenase and kynurenine aminotransferase, toll-like receptors (TLR) 4 and TLR9, and the fractalkine receptor CX3CR1 (reviewed by Hopper *et al*[17]), while general therapeutics are mainly limited to non-steroid anti-inflammatory drugs[18]. In our experiments, anti-inflammatory and membrane-stabilizing lipid N-stearoylethanolamine was an efficient drug to prevent and cure neuroinflammation-related cognitive impairment[19].

NICOTINIC ACETYLCHOLINE RECEPTORS OF α7 SUBTYPE: ROLE IN COGNITION/MEMORY AND INFLAMMATION

Nicotinic acetylcholine receptors of α7 subtype (α7 nAChRs) play a substantial role in controlling neuroinflammation. These receptors are abundantly expressed within the brain in neurons, astrocytes, and microglia[20-22]. In addition to the cell plasma membrane, they are found in the outer membrane of mitochondria where they regulate the release of pro-apoptotic factors like cytochrome c and, therefore, control the mitochondrial pathway of apoptosis[23]. The α7 nAChRs are involved in the cholinergic anti-inflammatory pathway by attenuating the production of pro-inflammatory cytokines IL-1β, IL-6, or TNF-α[24,25]. They are shown to regulate inflammatory reactions in the brain[26], support the viability of brain neurons[27], and directly interact with amyloid β (Aβ)–the main pathogenic factor upon Alzheimer disease[28]. Many experimental data demonstrate that α7 nAChRs are involved in essential cognitive functions such as memory, thinking, comprehension, learning capacity, calculation, orientation, and language[29-31]. Experiments from our laboratory demonstrated that neuroinflammation induced by intraperitoneal injections of bacterial LPS in mice caused down-regulation of α7 nAChRs, accumulation of Aβ within the brain, and episodic memory impairment. A similar effect could be achieved with the antibody against extracellular domain of α7 nAChR subunit[12]. Mutant mice lacking α7 nAChRs possessed elevated IL-1β in the blood and demonstrated worse episodic memory compared to their wild-type counterparts[32]. Neuroinflammation decreased the level of α7 nAChRs and stimulated accumulation of $A\beta_{1-42}$ in the brain mitochondria resulting in increased sensitivity of mitochondria to apoptogenic stimuli [33]. Taken together, these data demonstrate a critical role of α7 nAChR in neuroinflammation and relative cognitive impairment[31]. Correspondingly, one of the strategies to overcome the negative consequences of neuroinflammation is either activating or up-regulating α7 nAChRs. The former is achieved with selective agonists or positive allosteric modulators[34,35], while the latter was discovered by our laboratory with N-stearoylethanolamine[19] or mesenchymal stem cells (MSCs)[36] (Figure 1).

THERAPEUTIC POTENTIAL OF MSCs UPON NEUROINFLAMMATION

General information

MSCs are multipotent cells capable of differentiating into various cell types (mainly adipo-, chondro- and osteocytes, but also neurons) and producing multiple growth and neurotrophic factors necessary for neurogenesis, neuroprotection, neovascularization, and induction of axonal sprouting[37,38]. They can be isolated from many tissues, including bone marrow, adipose tissue, skeletal muscle, heart, umbilical cord, and placenta. Due to low expression of major histocompatibility complex class I molecules, MSCs seem to avoid immune rejection; therefore, allogenic and even xenogeneic MSCs have been widely used in experiments and clinical trials of regenerative medicine to restore the damaged tissues, including the brain[39,40].

MSCs use upon neuroinflammation and in AD models

MSCs were shown to attenuate neuroinflammation[41]. Pre-clinical and clinical trials have indicated that intravenous injection of MSCs following stroke and spinal cord injury may significantly improve clinical outcomes[42]. Also, the beneficial role of transplanted MSCs in neurodegenerative diseases has been documented[37,43,44]. Using MSCs in experimental AD models show their capacity to protect brain cells from the Aβ cytotoxicity, attenuate neuroinflammation, and improve cognitive functions of mice and rats. Intracerebral transplantation of the syngeneic bone marrow-derived MSCs into Aβ -injected mice or transgenic amyloid precursor protein (APP)/presenilin 1 (PS1) mice resulted in the reduction of Aβ deposits, decreased inflammation, improved cognitive functions[45-47], and decreased cell damage in the hippocampus[48]. Positive effects were also observed if bone marrow MSCs were injected intravenously[49] or even delivered intranasally[50]. MSCs derived from adipose tissue were also found to decrease Aβ accumulation, improve memory[51,52], and stimulate neurogenesis[53] in transgenic APP/PS1 or Tg2576 mice. Human umbilical cord-derived MSCs decreased inflammation and improved memory in APP/PS1 mice[40] and in bulbectomized mice[54]; when induced to differentiate into neuron-like phenotype, they attenuated neuroinflammation and improved cognitive

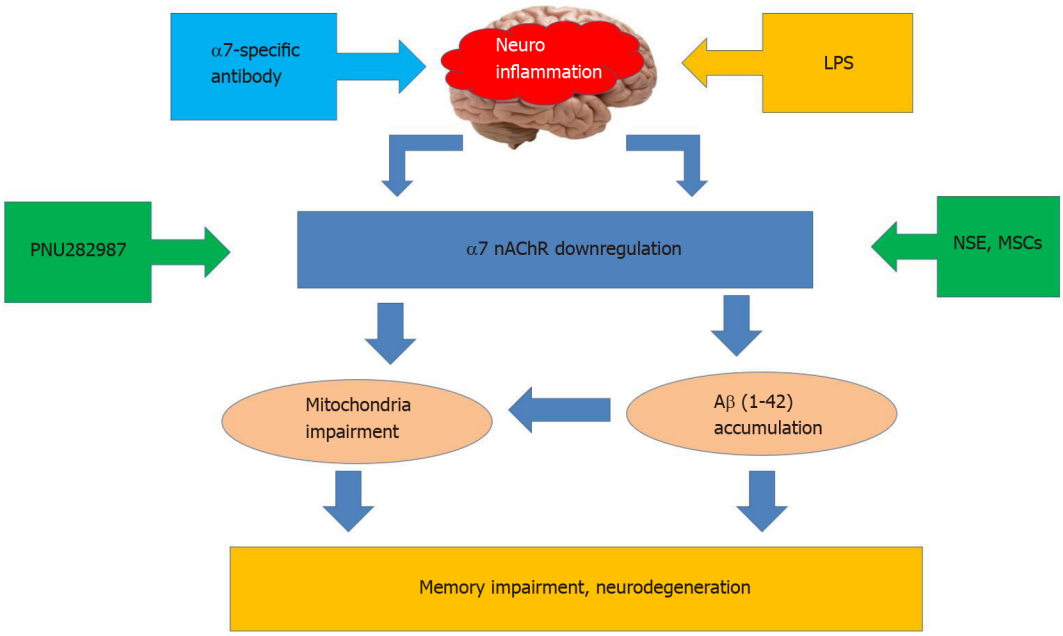

Figure 1 Scheme demonstrating the nicotinic acetylcholine receptors of α7 subtype involvement in the development of cognitive impairment upon neuroinflammation and positive effects of nicotinic acetylcholine receptors of α7 subtype-specific agonist PNU282987, N-stearoylethanolamine and mesenchymal stem cells. α7 nAChR: Nicotinic acetylcholine receptors of α7 subtype; LPS: Lipopolysaccharide; MSCs: Mesenchymal stem cells; NSE: N-stearoylethanolamine.

functions in APP/PS1 mice[41]. Placenta-derived MSCs attenuated Aβ accumulation and cognitive impairment and decreased the production of inflammatory cytokines and cell death in mice intracerebroventrically injected with $A\beta_{1-42}$[55]. Human amniotic MSCs transplantation into the hippocampus dramatically reduced Aβ deposition and rescued spatial learning and memory deficits in APP/PS1 mice[56]. MSCs inhibited the inflammatory response, microglia activation, neuronal damage, blood-brain barrier destruction, and viral load in mice infected with Japanese encephalitis virus[57]. These data indicate that both local and systemic infusions of MSCs of various origin had a stable therapeutic effect.

The use of MSCs in regenerative medicine is a rapidly developing field with dozens of new papers appearing each month. Further, I will summarize the data that were published during the last 2 years (2019-2020) and analyze the trends and perspectives of this research with regard to neuroinflammation and related disorders.

MSCs targets and treatment consequences

Experiments were performed in order to identify the main targets and mechanisms of MSC-mediated effects in the brain. Specific attention was paid to microglia, which control brain inflammatory reactions. Microglia, similarly to peripheral macrophages, can be represented by either M1 (pro-inflammatory) or M2 (anti-inflammatory) phenotypes. MSCs promoted M2 polarization and inhibited M1 polarization both *in vivo* and *in vitro*[58,59]. Activated microglia-mediated neuroinflammation involved in the pathogenesis of subarachnoid hemorrhage-induced brain injury could be alleviated by treatment with bone marrow MSCs[60]. MSCs also prevented astrogliosis, reduced messenger RNA expression of inflammatory cytokines, and promoted the acquisition of progenitor traits by astrocytes in experimental autoimmune encephalomyelitis mice, an animal model of multiple sclerosis[61]. The bone marrow MSCs regulated neuroinflammation in mice with postoperative inflammatory syndrome by affecting transforming growth factor-β levels[62]. MSCs reduced stress-induced circulating proinflammatory cytokines, monocytes, neuroinflammation, and depressive and anxiety-like behaviors such as major depressive disorder[63]. Neuroinflammation along with peripheral TNF-α elevation is associated with schizophrenia-relevant behaviors. Human umbilical cord MSCs inhibited schizophrenia-relevant and neuroinflammatory changes in amphetamine-sensitized mice, the main mechanism being associated with the induction of regulatory T cells and production of the anti-inflammatory cytokine IL-10 in the periphery[64].

In models of neurodegenerative diseases, it was also shown that a major mechanism for the efficacy of MSC-based therapy is immunoregulation, which modulates the activity state of microglia or astrocytes[65]. It was shown that MSC treatment resulted in the reduction of neuroinflammation, elimination of amyloid-β and neurofibrillary tangles, recovery of the blood-brain barrier and mitochondrial functions, up-regulation of acetylcholine levels, and improved cognition in AD models (reviewed in Kim *et al* [66]). The use of *in vitro* cell line model for AD, where bone marrow-derived MSCs were co-cultured with Aβ-treated neural cells, led to the identification of signaling pathways triggered by MSC-derived factors. It was found that MSC co-culture significantly changed the gene and protein expression of mammalian target of rapamycin, adenosine monophosphate-activated protein kinase, glycogen synthase kinase-3β, and Wnt3/β-catenin signaling pathways components in nerve cells[67]. The mechanisms of MSCs in Parkinson's disease, including growth factor secretion, exocytosis, and attenuation of neuroinflammation, have been reviewed in Chen *et al* [68]. Adipose tissue-derived MSCs were able to correct the imbalance between pro-inflammatory Th17 and regulatory T cells in the blood of Parkinson's disease patients [69]. MSCs restored microglia in the striatum and downregulated gene expression of inflammatory modulators in the brain of mice with experimental Huntington disease [70]. The main targets of MSCs related to neuroinflammation and studies during the last 2 years are summarized in Table 1.

Optimization of MSCs use for therapeutic purposes

MSCs isolated from tissues are usually maintained in culture for several passages before transplantation. It was found that long passaging may result in age-dependent decline in their function (reviewed in Fathi and Farahzadi[71]). For example, human adipose tissue-derived and bone marrow-derived MSCs show senescence signs after the eighth and seventh passage *in vitro*, respectively[72,73]. Senescence is usually accompanied by reduction of MSC proliferation potential that may be due to telomere shortening[74]. Therefore, the MSC aging status should be considered while using MSCs for therapeutic purposes. For example, we observed the increase of nAChR expression in cultured human umbilical cord-derived MSCs between the second and ninth passages *in vitro* that could reflect the loss of their stem cell properties (unpublished observation). Therefore, in our experiments, MSCs after the second passage *in vitro* have been used[32,36]. Aged MSCs may be used after reducing their senescence, for example, by retroviral transduction of the telomerase gene or culturing with growth factors *in vitro*[75]. One of the trends of recent studies is the use of "pre-conditioned" MSCs, which were pre-incubated with various physical, chemical, or biological factors before infusion into the host[76,77]. The popular idea is to use hypoxic conditions, because hypoxic micro-environment is physiologically normal for MSCs *in vivo*[58], while culturing in a normoxic atmosphere (21% O_2) promotes the generation of reactive oxygen species and premature senescence[73]. Previous studies demonstrated that culturing human MSCs under hypoxic condition was accompanied by increased telomerase activity, increased lifespan, and maintained stem cell properties of MSCs[73,75]. Hypoxia preconditioning stimulated the migration of transplanted MSCs into the brain and promoted neurogenesis and neurological functional recovery upon intracerebral hemorrhagic stroke[78]. In a recent paper, soluble factors derived from human adipose MSCs, preconditioned with either hypoxia-mimetic deferoxamine or pro-inflammatory cytokines (TNF-α + interferon-γ), reversed asphyxia-induced oxidative stress in the hippocampus and reduced neuroinflammation, resulting in improvement of locomotor and cognitive activity[79].

Another study used tanshinone IIA, an active compound from the root of Salvia plant, which possesses acetylcholinesterase inhibitory activity. It was found that tanshinone IIA-treated MSCs had greater neuroprotective effects than non-treated MSCs against neurotoxicity in the rat hippocampus by suppressing $A\beta_{25-35}$-induced neuroinflammation[80]. This result is in line with the role of nicotinic acetylcholine receptors (activated by acetylcholine) in neuroinflammation discussed above; it indicates that acetylcholine produced by MSCs may be one important factor of their regenerative capacity.

Another approach to improve the effects of MSCs is to use genetically modified MSCs, in which anti-inflammatory cytokines like IL-10 are overexpressed. It was found that transplantation of IL-10-expressing MSCs significantly reduced the number of dead cells in the cortex and hippocampus of rats after traumatic brain injury compared to non-modified MSCs. Rats transplanted with MSCs-IL-10 demonstrated increased autophagy, mitophagy, and cell survival markers, along with decreased markers for cell death and neuroinflammation[81].

Table 1 Neuroinflammation-related cognitive disorders treated with mesenchymal stem cells

Neurological pathology	Ref.
Hemorrhage-induced brain injury (stroke)	Chang *et al*[42], 2014
	Liu *et al*[60], 2019
Traumatic brain injury	Tsai *et al*[75], 2011
Post-operative inflammatory syndrome	Sun *et al*[62], 2020
Experimental autoimmune encephalomyelitis	Vigo *et al*[61], 2021
Major depressive disorder	Gallagher *et al*[63], 2019
Schizophrenia-relevant behavior	You *et al*[64], 2020
Neurodegenerative diseases	Sakthiswary and Raymond[37], 2012
	Kim *et al*[43], 2013
	Fan *et al*[44], 2014
	Zhang *et al*[65], 2020
AD models	Lee *et al*[39], 2012
	Yang *et al*[41], 2013
	Lee *et al*[45], 2009
	Lee *et al*[46], 2010
	Bae *et al*[47], 2013
	Zhang *et al*[48], 2012
	Salem *et al*[49], 2018
	Danielyan *et al*[50], 2014
	Ma *et al*[51], 2013
	Chang *et al*[52], 2014
	Yan *et al*[53], 2014
	Bobkova *et al*[54], 2013
	Yun *et al*[55], 2013
	Zheng *et al*[56], 2017
	Bian *et al*[57], 2017
	Kim *et al*[66], 2020
	Farahzadi *et al*[67], 2020
	Dando *et al*[82], 2014
PD models	Chen *et al*[68], 2020
	Bi *et al*[69], 2020
Huntington disease	Yu-Taeger *et al*[70], 2019

AD: Alzheimer diseases; PD: Parkinson diseases.

An important role is played by the route of MSC infusion. A targeted intracranial transplantation is efficient but quite traumatic, while a routine intravenous injection does not always result in efficient homing of injected MSCs to the brain. Several studies showed that MSCs injected intravenously are accumulated in the periphery, mainly in lung[63]. In our experiments, fluorescently-labeled MSCs, injected intravenously, were found in the brain parenchyma of LPS-treated mice[36], and α7+ MSCs obtained from either human umbilical cord or mouse placenta were found in the hippocampus of α7-/- mice on days 7 and 14 after intravenous injection[32], probably, due to impairment of the blood-brain barrier caused by inflammation. Currently, one of the perspective routes is intranasal administration of MSCs. This procedure is non-

invasive and, most importantly, facilitates efficient MSCs trafficking into the brain through the olfactory system, which bypasses the cellular barriers of the central nervous system and provides a direct portal from the nasal cavity to the olfactory bulb within the brain[82]. It was found that MSCs reached the hypoxia-ischemic lesion site in the brain within just 2 h after intranasal administration, reaching peak accumulation at 12 h. The MSC-treatment resulted not only in the decrease of reactive astrocytes and microglia, and polarization of microglia towards the M2 phenotype, but also induced a cascade of events leading to tissue repair including the attraction and maturation of neuroblasts[83].

Mediators of MSCs stimulating activity

One of the crucial questions arising from the application of MSCs is whether their therapeutic effect is solely due to humoral secreted factors or if MSCs realize their multipotent potential and substitute the damaged brain cells of the host. In our experiments, xenogeneic (human) MSCs were almost as efficient as allogeneic (mouse) cells and injections of human MSC-conditioned medium also produced a positive effect in LPS-treated mice. Either human MSCs or their supernatants up-regulated α4, α7, α9, β2, and β4 nAChR subunits and decreased the level of $A\beta_{1-42}$ in their brains[36]. However, in contrast to cells that supported memory of LPS-treated mice for months, the effect of a single injection of conditioned medium was transient and disappeared after 2 wk. Either intravenously injected MSCs or intraperitoneally injected human MSCs-conditioned medium transiently improved episodic memory of α7-/- mice[32]. In other experiments, conditioned medium of adipose tissue-derived MSCs improved memory deficit, decreased beta amyloids formation, increased neuron survival, and attenuated inflammation by reducing the expression of TLRs in rats AD model[84]. These data indicate that the positive effect observed is due to soluble factors produced by MSCs, and this effect is prolonged when injected MSCs home to the host's brain. We also identified that either MSCs or their conditioned medium stimulated an IL-6 increase in the brain, which coincided with the improvement of episodic memory; injections of recombinant IL-6 also improved episodic memory of α7-/- mice accompanied by the up-regulation of α3, α4, β2, and β4 nAChR subunits in the brain [32]. Therefore, IL-6 (in physiological concentrations) can be regarded as one of pro-cognitive factors either directly produced or stimulated by MSCs.

MSCs extracellular vesicles

The idea of using MSC conditioned medium instead of cells is attractive because it simplifies the therapeutic procedure and eliminates the potential for an immune reaction if using allogenic MSCs. The results of multiple studies published during the last 2 years demonstrate that soluble factors produced by MSCs are stored and released in the form of extracellular vesicles (EVs) or exosomes, the membrane nanostructures containing proteins, lipids, and nucleic acids, which possess properties similar to the cells from which they are derived but have lower immunogenicity and are capable of crossing the blood-brain barrier. Experimental studies showed that EVs have immunomodulatory and neuroprotective properties; they can stimulate neurogenesis and angiogenesis[85]. Exosomes derived from umbilical cord MSCs dampened the LPS-induced inflammation in microglial cells. When intranasally administered, they reached the brain and reduced microglia-mediated neuroinflammation in rats with perinatal brain injury[86]. Exosomes originating from hypoxic preconditioned MSCs repaired traumatic spinal cord injury[58]. MSC-derived exosomes inhibited early neuroinflammation after traumatic brain injury in mice[87] and reduced neuroinflammation in aged rhesus monkeys with cortical injury[88]. Intranasally administered MSC-derived EVs reached the brain, dampened the activation of microglia cells, and increased dendritic spine density in AD transgenic mice[89]. Many studies using MSC-derived EVs showed that they polarized *in vitro* microglia/macrophages toward an anti-inflammatory phenotype, suggesting that the neuroprotective effects could result from a modulation of the inflammatory status[58, 87,88]. Exosomes interfered with the TLR4 signaling in microglia prevented the degradation of the nuclear factor-kappa B inhibitor IκB-α and phosphorylation of molecules of the mitogen-activated protein kinase family in response to LPS stimulation[86]. Exosomes from hypoxia-pre-conditioned MSCs were shown to contain microRNA miR-216a-5p, which could modulate microglial polarization through TLR4/nuclear factor-kappa B/phosphoinositol-3-kinase/AKT signaling cascade[58]. In addition, MSC-exosomes inhibited the expression of pro-apoptosis protein Bax and pro-inflammatory cytokines, TNF-α and IL-1β, while enhancing the expression of the anti-apoptosis protein Bcl-2[87] and, therefore, supported brain cell viability.

CONCLUSION

Taken together, the data reviewed demonstrate that MSCs have a significant therapeutic potential in treating neuroinflammation-related disfunctions including cognitive and age-related neurodegenerative diseases. Although MSCs of various origin were found to be efficient in alleviating neuroinflammation, the use of autologous blood- or adipose tissue-derived MSCs seems mostly preferable, because these cells can be isolated from the patient at any time and with reasonable traumatic interventions. In contrast, placenta- or umbilical cord-derived MSCs should be collected and stored for potential future use. The low immunogenicity of MSCs may allow using allogenic cells from general cell banks. The therapeutic effect of MSCs is mainly mediated by soluble growth, neurotrophic, and survival factors, which are secreted in the form of nanovesicles (EVs). However, maximal therapeutic effect is being achieved when MSCs penetrate the brain and produce their stimulating factors *in situ*. MSCs accumulated in the brain not only dampen neuroinflammation but attract host neuronal cell progenitors to the lesion site and stimulate their differentiation. Optimization of MSCs use for therapeutic purposes should include measures to facilitate their homing to the brain, support the survival in the brain microenvironment, and stimulate the production of neurotrophic and anti-inflammatory factors. The intranasal route of infusion seems to be advantageous, because it is the least traumatic and ensures fast MSCs transportation to the brain.

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