

Review

Optimal mesenchymal stem cell delivery routes to enhance neurogenesis for the treatment of Alzheimer's disease

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Summary. Alzheimer's disease (AD) is a common cause of dementia. Alzheimer's disease (AD) is characterized by progressive loss of memory in addition to cortical atrophy. Despite decades of research and therapeutic trials in AD, an effective treatment is yet to be developed. Mesenchymal stem cells (MSCs) have emerged as promising tools for the treatment of AD, and clinical trials have been completed or are in progress. MSCs secrete various cytotropic factors that may exert beneficial effects in AD. The route of administration is an important factor to enhance MSC based treatment effects for AD. Among various routes, the intracerebroventricular route may possess several advantages such as the activation of neurogenesis, compared to other routes for AD treatments. In this review, we will focus on recent pre-clinical and clinical advances in MSC-based treatment of AD, specifically in relation to enhancement of endogenous neurogenesis.

Key words: MSCs, Alzheimer's disease, Delivery route, Neurogenesis

Introduction

Alzheimer's disease (AD) is a widespread cause of dementia (Burns and Iliffe, 2009). AD is an age-related, progressive, and irreversible neurodegenerative disease (Selkoe, 2001; Bartzokis, 2004; Keller, 2006). The pathological features of AD include amyloid-beta ($A\beta$) plaque formation, neuronal loss, and tau hyperphosphorylation that result in cortical atrophy, progressive loss of memory, and severe cognitive impairment (Keller, 2006; Nistor et al., 2007; Vestergaard et al., 2008; Burns and Iliffe, 2009; Tanna and Sachan, 2014).

Despite decades of research and therapeutic trials in AD, an effective treatment is yet to be developed (Cummings et al., 2014; Schneider et al., 2014). Current Food and Drug Administration-approved treatments temporarily delay the progression of AD (Schneider and Sano, 2009). Furthermore, most treatments that are being developed are single-targeted for amyloid beta ($A\beta$) (Miller, 2010; Jia et al., 2014). The development of a multi-target drug, however, may be more effective considering the multiple pathogenic mechanisms of AD.

Mesenchymal stem cells (MSCs) are multipotent stem cells that are capable of self-renewal and differentiation into various cell types (Caplan, 1991). MSCs act primarily through trophic support that appears to be mediated by direct and indirect actions (Caplan and Dennis, 2006; Scuteri et al., 2014). MSCs secrete various cytotropic factors which, in mouse models of AD, have benefits that include reducing amyloid burden, modulating inflammation, and increasing endogenous

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neurogenesis (Kim et al., 2012, 2015a; Lee et al., 2012; Park et al., 2016b). Especially, MSC treatment has received considerable attention as a potential AD therapeutic option to improve neurogenesis, and studies using animal models have shown promising results (Kim et al., 2015a; Park et al., 2016b).

In mammals, adult neurogenesis occurs in two areas of the central nervous system (CNS): the subventricular zone (SVZ) and subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Reynolds and Weiss, 1992; Richards et al., 1992). In both areas, neurogenesis progresses as a complex, multi-stage process, which starts with the proliferation, migration, and differentiation of neural precursors (Eriksson et al., 1998; Ming and Song, 2005; Zou et al., 2010) to regenerate cortical neurons. Therefore, neurogenesis must be activated to regenerate cortical neurons (Kriegstein and Alvarez-Buylla, 2009; Christie and Turnley, 2012; Saha et al., 2012; Ohira et al., 2013) and improve memory function (Bruel-Jungerman et al., 2007; Deng et al., 2010; Kitamura and Inokuchi, 2014).

Subsequently, many groups have proposed that improving adult neurogenesis leads to the development of therapeutic strategies for a wide array of diseases where abnormal adult neurogenesis is present such as AD (Kim et al., 2015a; Park et al., 2016b), Parkinson's disease (Winner et al., 2009; Regensburger et al., 2014), Huntington's disease (Curtis et al., 2003) and stroke (Marlier et al., 2015).

Improvement of neurogenesis is dependent on the delivery of MSCs into the AD brain. The route of administration is an especially important factor that can enhance the beneficial effects of MSCs for AD treatment (Misra et al., 2003; Park et al., 2016a). According to recent studies, one of the optimal routes is the intracerebroventricular (ICV) route which can effectively deliver more MSCs to the SVZ where neurogenesis occurs.

In this review, we will focus on recent pre-clinical and clinical advances in MSC-based treatment of AD, specifically in relation to enhancement of endogenous neurogenesis.

AD clinical trials involving MSCs

Ten clinical trials of AD treatments have been completed or are in progress. These trials utilize various delivery routes to administer MSCs and therapeutic potential and clinical accessibility are also assessed (Kim et al., 2015b). All have successfully met safety concerns. In most of these trials, MSCs were given via intravenous, intraparenchymal, or ICV routes. We will focus on the progress of clinical trials based on the route of administration. Clinical studies that have delivered MSCs in AD patients are summarized in Table 1.

Intravenous transplantation

Six of ten clinical trials are in advanced stages or

have been completed, with intravenously injected MSCs. In a phase I clinical trial study (Clinicaltrials.gov NCT02600130) conducted in the United States of America (USA), allogenic, human bone marrow-derived MSCs (hBM-MSCs) were intravenously injected as single cells according to the criteria of the National Institute of Neuropsychological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). The trial is scheduled to end in October 2019. Subjects were divided into a high-dose (10×10^7 cells), low-dose (2×10^7 cells), or a placebo group. This phase I study compared blood and cerebrospinal fluid (CSF), calculated brain volumetry using Magnetic Resonance Imaging (MRI), and conducted neuropsychological assessments before and after injection to evaluate safety and efficacy.

In a phase IIa clinical trial study (Clinicaltrials.gov NCT02833792) conducted in the USA, allogenic, hBM-MSCs were single intravenously injected in subjects diagnosed with mild to moderate dementia and probable AD according to the criteria of the NINCDS-ADRDA. The trial is scheduled to end in June 2018. Subjects were divided into a stem cell injection group (1.5×10^6 cells/kg body weight) or a placebo group. This phase IIa study also includes neuropsychological assessments which are performed before and after injection to evaluate safety and efficacy.

In a phase I/II clinical trial study (Clinicaltrials.gov NCT03117738) conducted in the USA, autologous, human adipose-derived MSCs (hAD-MSCs) were intravenously injected nine times into subjects with probable AD according to the criteria of the NINCDS-ADRDA. The trial is scheduled to end in November 2018. Subjects were divided into a stem cell injection or a placebo group. This phase I/II study compares electrocardiogram (ECG), MRI, and A β biomarkers. Neuropsychological assessments are performed before and after injection to evaluate safety and efficacy.

In a phase I/II clinical trial study (Clinicaltrials.gov NCT02899091) conducted in South Korea, allogenic, human placenta-derived MSCs (hPL-MSCs) were intravenously injected twice in subjects with probable AD according to the criteria of the NINCDS-ADRDA. The trial is scheduled to end in June 2018. Subjects were divided into a stem cell injection (2×10^8 cells) or a placebo group. This phase I/II study compares A β and tau levels in CSF, brain MRI, amyloid positron emission tomography (PET), quantitative electroencephalography (qEEG), and neuropsychological assessments which are performed before and after injection to evaluate safety and efficacy.

In a phase I/II clinical trial study (Clinicaltrials.gov NCT01547689) conducted in China, allogenic, human umbilical cord Wharton's jelly-derived MSCs (hUC-MSCs) (2×10^7 cells) were intravenously injected eight times in subject with probable AD according to the criteria of the NINCDS-ADRDA. The trial is scheduled to end in December 2016. The trial is still active but not

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recruiting participants currently. This phase I study compares A β and tau levels in CSF, Th1/Th2 cytokines in the peripheral blood, and neuropsychological assessments are performed before and after injection to evaluate safety and efficacy.

In a phase I/II clinical trial study (Clinicaltrials.gov NCT02672306) conducted in China, allogenic, hUC-MSCs (2×10^6 cells) were intravenously injected eight

times in subjects with probable AD according to the criteria of the NINCDS-ADRDA. The trial is scheduled to end in October 2019. Subjects are divided into a stem cell injection (2×10^6 cells) or a placebo group. This phase I study compares A β levels in the blood, A β and tau levels in the CSF, and neuropsychological assessments are performed before and after injection to evaluate safety and efficacy.

Table 1. MSC clinical trials involving AD patients (registered on Clinicaltrials.gov).

Injection Route	Trial ID	Nation	Study date	Type of trial	Cell source	Arm	Outcome	Status
Intravenous	NCT02600130	USA	2016.8~2019.10	Phase I	hBM-MSCs Allogenic	n=30 Single injection Gr 1: 2×10^7 Cells Gr 2: 10×10^7 Cells Gr 3: Placebo	•Safety: 30 days from post-administration •Efficacy: At baseline, 2, 4, 13, 26, 39, and 52 weeks	Recruiting
Intravenous	NCT02833792	USA	2016.6~2018.6	Phase IIa	hBM-MSCs Allogenic	n=40 Single injection Gr 1: 1.5×10^6 cells per kilogram body weight Gr 2: Placebo	•Safety: 18 months from post-administration •Efficacy: 18 months from post-administration	Recruiting
Intravenous	NCT01547689	China	2012.3~2016.12	Phase I/II	hUC-MSCs Allogenic	n=30 Repeated injection (8 times, Once every two weeks in the first month of each quarter injection) Gr 1: 2×10^7 Cells	•Safety: 10 weeks from post-administration •Efficacy: 10 weeks from post-administration	Active, not recruiting
Intravenous	NCT02672306	China	2016.5~2019.10	Phase I/II	hUC-MSCs Allogenic	n=40 Repeated injection (8 times at 2 week intervals) Gr 1: 2×10^6 Cells Gr 2: Placebo	•Safety: 10 weeks from post-administration •Efficacy: 10 weeks from post-administration	Not yet recruiting
Intravenous	NCT03117738	USA	2017.4~2018.11	Phase I/II	hAD-MSCs, Autologous	n=60 Repeated injection (9 times at 2 week intervals) Gr 1: MSCs injection Gr 2: Placebo	•Safety: 32 weeks from post-administration •Efficacy: 32 weeks from post-administration	Recruiting
Intravenous	NCT02899091	Korea	2016.9~2018.6	Phase I/IIa	hPL-MSCs Allogenic	n=24 Repeated injection (2 times at 4 week intervals) Gr 1: 2×10^8 Cells Gr 2: Placebo	•Safety: 48 weeks from post-administration •Efficacy: 48 weeks from post-administration	Not yet recruiting
Intracerebral	NCT01297218	Korea	2011.2~2011.9	Phase I	hUCB-MSCs Allogenic	n=9 Single injection Gr 1: 3×10^6 Cells Gr 2: 6×10^6 Cells	•Safety: 12 weeks from post-administration •Efficacy: 12 weeks from post-administration	Completed
Intracerebral	NCT01696591	Korea	2012.3~2013.9	Phase I	hUCB-MSCs Allogenic	n=14 Single injection Gr 1: 3×10^6 Cells Gr 2: 6×10^6 Cells	•Safety: 24 months from post-administration •Efficacy: 24 months from post-administration	Completed
ICV	NCT02054208	Korea	2014.2~2019.7	Phase I/IIa	hUCB-MSCs Allogenic	n=45 Repeated injection (3 times at 4 week intervals) Gr 1: 1×10^7 Cells Gr 2: 3×10^7 Cells Gr 3: Placebo	•Safety: 24 weeks from post-administration •Efficacy: 24 weeks from post-administration	Recruiting
ICV	NCT03172117	Korea	2017.5~2021.12	Phase I/IIa	hUCB-MSCs Allogenic	n=45 Repeated injection (3 times at 4 week intervals) Gr 1: 1×10^7 Cells Gr 2: 3×10^7 Cells Gr 3: Placebo	•Efficacy: 24 weeks from post-administration	Recruiting

AD: Alzheimer's disease, Gr: Group, hAD-MSCs: Human adipose-derived mesenchymal stem cells, hBM-MSCs: Human bone marrow-derived mesenchymal stem cells, hPL-MSCs: Human placenta-derived mesenchymal stem cells, hUC-MSCs: Human umbilical cord Warton's jelly-derived mesenchymal stem cells, hUCB-MSC: Human umbilical cord blood-derived mesenchymal stem cells, ICV: Intracerebroventricular, MSCs: mesenchymal stem cells.

Intra-parenchymal transplantation

Two of ten advanced or completed AD clinical trials using MSCs involve intra-parenchymal injection.

In phase I clinical trial studies (Clinicaltrials.gov NCT01297218, NCT01696591) conducted in South Korea, allogenic, human umbilical cord blood-derived MSCs (hUCB-MSCs) were applied to nine patients with probable AD according to the criteria of the NINCDS-ADRDA and dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). These trials were scheduled to end in September 2011 and September 2013 respectively. Subjects were divided into a stem cell high-dose (6×10^6 cells, $n=6$), low-dose (3×10^6 cells, $n=3$), and conventionally treated group. hUCB-MSCs were delivered via stereotactic injection into the bilateral hippocampus and precuneus. These phase I studies have compared A β and tau levels in the CSF, Pittsburgh compound B (PIB)-positron emission tomography (PET), 18F-fluorodeoxyglucose (FDG)-PET, and neuropsychological assessments were also conducted before and after injection to evaluate safety and efficacy. The researchers found no severe acute or long-term side effects or significant clinical efficacies based on the evaluated measurements (Kim et al., 2015b).

ICV transplantation

Two of ten advanced or completed AD clinical trials using MSCs involved ICV injections.

In phase I/IIa clinical trial studies (Clinicaltrials.gov, NCT02054208, NCT03172117) conducted in South Korea, allogenic hUCB-MSCs were injected three times via the ICV route in subjects with probable AD according to the criteria of the NINCDS-ADRDA. These trials are scheduled to end by July 2019 and December 2021 respectively. Subjects were divided into two stages. Stage 1 included nine subjects: three will receive a low dose (1×10^7 cells) and six will receive a high dose (3×10^7 cells). Stage 2 included 36 subjects: 12 were placebo and 24 received high doses of MSCs. hUCB-MSCs were injected into the ventricle using an ommaya reservoir. These phase I/IIa studies compared CSF biomarkers, florbetaben-PET, FDG-PET scans, and neuropsychological assessments were completed before and after injection to evaluate safety and efficacy.

Pre-clinical studies of MSCs delivery routes for AD treatment

MSCs can be administered into the brain intravenously, intra-arterially, intraventricularly, via the spinal cord, and also directly through the intra-parenchymal route. These routes differ from one other in terms of their degree of invasiveness (or convenience), area of cell distribution, and accessibility to the brain (Misra et al., 2003). Also, due to the time-limited

survival of MSCs within the brain (Kurtz, 2008; Eggenhofer et al., 2014), optimal delivery via repeated administration needs to be determined for neurodegenerative chronic diseases such as AD (Misra et al., 2003; Taha, 2010).

In this section, we focus on pre-clinical studies that have investigated the effects on neurogenesis based on the delivery routes dealt by AD clinical trials in the previous section (Kim et al., 2015b). Pre-clinical studies that have administered MSCs into the transgenic AD models are summarized in Table 2.

Intravenous transplantation

In previous pre-clinical studies, intravenous injections were generally used to target the liver or lung but not the brain. However, single or repeatedly injected MSCs via the intravenous is reported to enhance neuroprotection (Yun et al., 2013; Misra et al., 2016), reduce oxidative stress (Cui et al., 2017), increase A β clearance (Nikolic et al., 2008; Shin et al., 2014), increase microglial phagocytic activity (Nikolic et al., 2008; Yun et al., 2013), and also promote neurogenesis (Yun et al., 2013; Shin et al., 2014; Cui et al., 2017) which improves the functional recovery of AD models. Regarding the distribution of intravenously injected MSCs into other organs excluding the brain of a transgenic AD mouse model, the highest numbers of cells were observed first in the liver and then the lung, and this number decreased as time progressed (Park et al., 2016c). Although not delivered to the brain, MSCs entrapped in other organs like the lung and liver can have a potential therapeutic role in the brain by the secretion of paracrine factors that can cross the blood brain barrier (Gao et al., 2001; Schrepfer et al., 2007; Park et al., 2016c).

Intravenous injection is the least invasive and the administration procedure is relatively simple compared to the other routes. Repeated injections are possible (Park et al., 2016c). However, it is doubtful whether the desired effect would occur, because the efficacy of paracrine factors released from organs other than the brain will be reduced once in contact with the systemic circulation. Therefore, it is difficult to expect activation of neurogenesis based on intravenously injected MSCs for the treatment of AD.

Intra-parenchymal transplantation

Based on previous pre-clinical studies, the intra-parenchymal route was utilized to deliver MSCs into targeted structures such as the hippocampus and precuneus. Injected MSCs affect AD pathology by the secretion of various cytotropic factors including intercellular adhesion molecule 1 (ICAM-1), chemokine (C-C motif) ligand 5 (CCL-5), interleukin (IL)-10 and -6, vascular endothelial growth factor (VEGF), transforming growth factor-beta 1 (TGF- β 1), glial cell-derived neurotrophic factor (GDNF), and brain-derived

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neurotrophic factor (BDNF) (Joyce et al., 2010; Kim et al., 2012; Lee et al., 2012; Kyurkchiev et al., 2014; Colpo et al., 2015). Through these trophic factors, MSCs activate microglia, increase A β degrading enzymes (Lee et al., 2010b; Kim et al., 2012; Lee et al., 2012; Yang et al., 2013; Yan et al., 2014), reduce oxidative stress (Lee et al., 2010a), apoptosis (Lee et al., 2010a), tau hyperphosphorylation (Kim et al., 2012), modulate immune mechanisms (Lee et al., 2010b; Colpo et al., 2015), and promote neurogenesis (Yan et al., 2014).

Learning ability and memory were also improved (Lee et al., 2009, 2010a, 2010b, 2012; Babaei et al., 2012; Yang et al., 2013).

Direct intra-parenchymal injection is the most effective route to deliver MSCs into a targeted structure. Activation of neurogenesis can also be expected following intra-parenchymal delivery. However, this injection requires brain surgery under general anesthesia, and so repeated injections of MSCs are impractical (Kean et al., 2013; Kim et al., 2015b).

Table 2. Pre-clinical studies that have delivered MSCs in AD models over the past 5 years.

Injection Route	Model	Mesenchymal Stem Cells	Dose	Number of injection	Efficacy & Mechanism	Efficacy Period	Ref
Intravenous	ICV-isoproterenol induced rat	rBM-MSCs	1 \times 10 ⁶ cells /500ul	Single	•Regain of memory •Neuroprotective	21days	Misra et al., 2016
Intravenous	Tg 2576 AD mice	hUC-MSCs	2 \times 10 ⁶ cells /200ul	Single	•Hippocampal neurogenesis •Up-regulation of neuronal synaptic plasticity •Decreased oxidative stress •Not significantly affect levels of A β and A β -degrading/ generating factors	28days	Cui et al., 2017
Intravenous	Tg APP/PS1 mice	hMSCs	1 \times 10 ⁶ cells /100ul	Single	•A β clearance •Enhanced autolysosome formation	4days	Shin et al., 2014
Intravenous	ICV-A β induced mice	hMSCs	2 \times 10 ⁶ cells /100ul	Single	•Hippocampal neurogenesis •Improved cognitive performance of memory	4weeks	Oh et al., 2015
Intravenous	Tg 2576 AD mice	hAD-MSCs	1 \times 10 ⁶ cells /150ul per times	13 times	•Decreased A β levels •Improved learning and memory	14months	Kim et al., 2012b
Intravenous	Tg APP/PS1 mice	hUCB-MSCs	1 \times 10 ⁶ cells /100ul	Single	•No efficacy	7days	Park et al., 2016
Intracerebral (Hippocampus)	1. Aged Rat 2. Ibotenic acid induced rat	hBM-MSCs	5 \times 10 ⁵ cells /1ul	Single	•Increased learning ability and memory	2months	Babaei et al., 2012
Intracerebral (Hippocampus bilaterally)	Tg APP/PS1 mice	hUCB-MSCs	1 \times 10 ⁴ cells /3ul	Single	•Decreased A β levels •Increased A β -degrading enzyme	7days	Kim et al., 2012a
Intracerebral (Hippocampus bilaterally)	Tg APP/PS1 mice	rBM-MSCs	2 \times 10 ⁴ cells	Single	•Recruitment for the alternated microglia activation; •Reduction in A β deposition and memory impairment	14days	Lee et al., 2012
Intracerebral (Hippocampus bilaterally)	Tg APP/PS1 mice	hUC-MSCs	5 \times 10 ⁴ cells /2ul	Single	•Improved cognitive function •Reduced A β deposition •Increased anti-inflammatory cytokine •Increased A β -degrading enzyme	3weeks	Yang et al., 2013
Intracerebral (Hippocampus bilaterally)	Tg APP/PS1 mice	rAD-MSCs	1 \times 10 ⁵ cells /3ul	Single	•Reduced oxidative stress in the hippocampus •Promote adult neurogenesis	4weeks	Yan et al., 2014
ICV (Ventricle)	Tg APP/PS1 mice	rBM-MSCs	1 \times 10 ⁶ cells /5ul	Single	•Reduced cognitive deficits •Recovering the innate interest to novelty and counteracting memory deficits	40days	Garcia et al., 2014
ICV (Ventricle)	3XTg-AD mice	hBM-MSCs	6 \times 10 ⁴ cells /2ul	Single	•Promote neurogenesis •Protective effects •Downregulation of A β 56 levels in the entorhinal cortex	6months	Ruzicka et al., 2016
ICV (Ventricle)	Tg 5XFAD mice	rBM-MSCs	4 \times 10 ⁵ cells /2ul	Single	•A β clearance •Reduced learning deficits	2~7months	Matchynski-Franks et al., 2016
ICV (Cisterna magna)	Tg APP/PS1 mice	hUCB-MSCs	1 \times 10 ⁵ cells /15ul per times	3times	•Promote neurogenesis	10weeks	Kim et al., 2015

A β : Amyloid beta, AD: Alzheimer's disease, hAD-MSCs: Human adipose-derived mesenchymal stem cells, hBM-MSCs: Human bone marrow-derived mesenchymal stem cells, hPL-MSCs: Human placenta-derived mesenchymal stem cells, hUC-MSCs: Human umbilical cord Warton's jelly-derived mesenchymal stem cells, hUCB-MSC: Human umbilical cord blood-derived mesenchymal stem cells, ICV: Intracerebroventricular, MSCs: mesenchymal stem cell, rAD-MSCs: Rodent adipose-derived mesenchymal stem cells, rBM-MSCs: Rodent bone marrow-derived mesenchymal stem cells, Tg: Transgenic.

ICV transplantation

In previous pre-clinical studies, ICV injection was used to deliver MSCs into the lateral ventricle near the SVZ. ICV administrated MSCs adhered to the ependymal cell layer and migrated from the ventricles to the brain parenchyma before being washed out by CSF flow (Park et al., 2016a). Single or repeated ICV injections of MSCs have therapeutic effects on reducing AD pathology by secretion of various cytotrophic factors such as growth differentiation factor-15 (GDF-15), Activin a, BDNF, and VEGF (Zhang et al., 2012; Garcia et al., 2014; Kim et al., 2015a; Park et al., 2016b). These trophic factors enhance neuroprotective effects (Garcia et al., 2014; Ruzicka et al., 2016), increase A β degrading enzymes (Kim et al., 2015a; Matchynski-Franks et al., 2016), promote synaptic activity (Kim et al., 2015a), hippocampal neurogenesis (Kim et al., 2015a), and SVZ neurogenesis (Kim et al., 2015a; Matchynski-Franks et al., 2016; Park et al., 2016a). All of these effects improve learning ability and memory in AD models (Zhang et al., 2012; Garcia et al., 2014; Matchynski-Franks et al., 2016).

ICV injection is similar to intra-parenchymal injection in that brain surgery must be performed under general anesthesia. After the first operation, repeated ICV injections can be easily done using the ommaya reservoir (Lee et al., 2014; Atkinson, 2017; Cohen-Pfeffer et al., 2017). Also, ICV administrated MSCs have been reported to activate neurogenesis in the SVZ and dentate gyrus where neural stem cells are maintained after embryonic development for the production of new cells in the brain (Conover and Notti, 2008; Tfilin et al., 2010; Kim et al., 2015a; Oh et al., 2015; Park et al., 2016b). Therefore, ICV administered MSCs show greater potential to regenerate cortical neurons and improve memory function via activation of neurogenesis and secretion of trophic factors.

Conclusion

According to clinical and pre-clinical trial for AD therapy using MSCs, the route of administration is an especially important factor that can enhance the beneficial effects of MSC-based AD therapy (Misra et al., 2003; Kim et al., 2015b; Park et al., 2016a). The limited number of optimal delivery routes has hindered the widespread application of MSCs in AD therapy. The blood brain barrier is a major obstacle that hinders the entry of MSCs into the brain (Liu et al., 2013; Aleynik et al., 2014). Also, due to the time-limited survival of MSCs within the brain (Kurtz, 2008; Eggenhofer et al., 2014; Ritfeld and Oudega, 2014), it is essential to investigate optimal delivery routes where repeated administrations are possible (Sanberg et al., 2012; Kean et al., 2013). Determination of the optimal route for MSC administration and understanding the underlying mechanism will improve the treatment of AD (Aleynik et al., 2014). Performing MSC-based therapy by utilizing

optimal delivery routes is poised to have a tremendous impact on the future of medicine by delivering more effective, safe and long-lasting therapies which will improve the quality of life condition for AD patients and caregiver.

Among these routes, the ICV route possesses several advantages compared to other routes. First, ICV injection is performed through the insertion of an ommaya reservoir (Adolph et al., 2010; Raffa and Pergolizzi, 2012), which is relatively less invasive and easier to administer repeated injections relative to intra-parenchymal injections. Compared to parenchymal injection where the distribution is focal, MSCs injected into the lateral ventricle can be distributed diffusely throughout the ventricle and to various parts of the brain including the hippocampus, which is located underneath the temporal horn of the lateral ventricle. Lastly, MSCs have been reported to activate endogenous neural stem cells in the SVZ and the dentate gyrus where neural stem cells are maintained after embryonic development for the production of new cells in the brain (Conover and Notti, 2008; Tfilin et al., 2010; Kim et al., 2015a; Oh et al., 2015).

In addition to satisfying the scientific basis of MSCs treatments, this approach will bring about viable options to overcome current limitations in MSCs therapy on AD. The implication of this approach in MSCs therapy is expected to modulate the outcome of intended therapy and should be a feasible cost-effective option for MSC-based regenerative therapies in the near future. Continuous effort is required to achieve a refined application of effective MSCs therapeutics for AD.

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Conflict of interest. None

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