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Review

Killing two birds with one stone: The multifunctional roles of mesenchymal stem cells in the treatment of neurodegenerative and muscle diseases

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Summary. Neurodegenerative and muscle diseases bear both complex and multifactorial pathologies. An efficacious and robust therapeutic option to treat these diseases is yet to be elucidated. At such a time, mesenchymal stem cells have drawn significant attention due to their immunomodulatory and regenerative properties. Accumulating evidence has proposed the capability of MSCs to serve multiple roles in a broad spectrum of diseases by secretion of trophic or paracrine factors. In the present review, we will look into the recent literature and discuss the therapeutic functions of MSCs and their potential to treat various neurodegenerative (Alzheimer's, Parkinson's, and Huntington's disease) and muscle (Duchenne muscular dystrophy, myopathy, and multiple sclerosis) diseases.

Key words: Mesenchymal stem cell, Muscle, Neurodegenerative, Paracrine, Therapeutic function

Introduction

Also referred to as "medicinal signaling cells", mesenchymal stem cells (MSCs) have gained recognition for their therapeutic capabilities in a wide array of diseases (Caplan, 2010, 2017a). MSCs can be easily isolated from fetal tissues such as wharton's jelly (WJ), umbilical cord blood (UCB), and placenta and also from adult tissues such as adipose, dental pulp, and bone marrow (BM) (Huang et al., 2009; Ma et al., 2014). Not only are MSCs freely accessible but they are also free from the ethical restraints that embryonic stem cells (ESCs) and induced-pluripotent stem cells (iPSCs) face. According to the criteria published by the International Society for Cellular Therapy (ISCT) in 2006, cells must meet the following criteria to be addressed as MSCs: (1) Cells must be able to adhere to the bottom of culture dishes (2) Although specific MSC markers are not present, in general, MSCs must positively express CD105, CD90, and CD73 antigens by ≥95% and barely express antigens such as HLA-DR, CD45, CD34, and CD14 by ≤10% (3) When induced *in vitro*, MSCs must be able to differentiate into adipocytes, chondrocytes, and osteocytes (Dominici et al., 2006). One major advantage of MSCs is that the cells lack the expression of MHC class II proteins (Ankrum et al., 2014; Shin et al., 2017), thus, problems of immune-rejection by the host is minimally if not at all encountered.

MSCs are proposed to exert their therapeutic functions through paracrine activity which involves the external secretion of cytokines or trophic factors. One prominent hypothesis is that MSCs normally exist as pericytes and when a lesion or damage occurs, these cells detach from blood vessels, become activated, migrate towards the lesion site through chemotaxis, and then secrete factors that serve a range of regenerative roles (Caplan and Dennis, 2006; Caplan and Correa, 2011; Caplan, 2017b) (Fig. 1). Immunomodulation is mediated by various soluble factors secreted by MSCs.

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Some examples of MSC-dervied factors which play a prominent role in immunosuppression are interleukin-6 (IL-6), heme oxygenase-1 (HO-1), transforming growth factor-beta (TGF-β), 2,3-dioxygenase (IDO), and nitric-oxide synthase (iNOS) (Ghannam et al., 2010; Ma et al., 2014). Out of the plethora of soluble factors secreted by MSCs, several factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and angiopoietin-1 (Ang-1) enhance endothelial cell proliferation which eventually promotes angiogenesis (Ma et al., 2014). Furthermore, MSCs are also capable of reducing levels of apoptosis. Stanniocalcin-1 (STC-1) is a well-known factor that was reported to reduce the apoptosis of lung cancer epithelial cells that have been exposed to hypoxic conditions (Block et al., 2009).

The paracrine activities of MSCs render them as beneficial for diseases characterized by complex mechanisms. For such diseases, single-targeted therapies will not be effective to alter the pathology and clinical course of a disease. In terms of drug development and research, undesirable and unsuccessful results have been met in treating complex diseases by utilizing only single-targeted agents (Lu et al., 2012). Neurodegenerative and muscle diseases are examples of these diseases characterized by unclear etiologies and complex pathophysiologies (Deconinck and Dan, 2007; Chin-Chan et al., 2015; Gitler et al., 2017). Predominantly through their paracrine activities, MSCs are capable of targeting a variety of mechanisms. Such therapeutic plasticity of MSCs make them strong candidates to confront the complex pathologies (Lewis and Suzuki, 2014) underlying neurodegenerative and muscle diseases.

In this review article, we will discuss the therapeutic roles of MSCs in tackling the multifaceted pathologies of neurodegenerative (Fig. 2) and muscle diseases (Fig. 3).

MSCs in the treatment of neurodegenerative diseases

Alzheimer's disease

Widely known as an age-related neurodegenerative disease, the occurrence of Alzheimer's disease (AD) is strongly associated with the aging population (Qiu et al., 2009; Johnson, 2015). Major pathological hallmarks of the disease include amyloid plaques generated from accumulation of beta amyloid (Aβ) proteins and neurofibrillary tangles created by a cluster of hyperphosphorylated tau proteins (Serrano-Pozo et al., 2011). The exact cause of the disease remains controversial and is yet to be elucidated. The amyloid cascade hypothesis supports the theory that the abnormal cleavage of the amyloid precursor protein (APP) by β and γ secretases unravels a chain of events which lead to neurotoxicity, neuronal loss, and eventually, dementia (Reitz, 2012; Selkoe and Hardy, 2016). Although a prominent hypothesis, clinical trials to this date have not brought forth definitive results to strongly support the claim that amyloid clearance is the optimal target to alter the clinical course of this devastating disease (Giacobini and Gold, 2013; Gold, 2017).

Considering the diverse and complicated pathology of AD, there are also suggestions that solely targeting amyloid will not serve as an effective therapeutic option to treat AD (Stephenson et al., 2015). MSCs have been proposed as an attractive candidate for AD stem cell therapy due to their multifaceted properties (Turgeman, 2015). Presumed to be exerted through their paracrine activities, when transplanted into a transgenic AD mouse model, MSCs have been reported to aid in Aβ removal, modulate immune responses, and exert neuroprotective effects. When directly injected into the hippocampi of the APP/Presenilin 1 (PS1) transgenic mouse model, human umbilical cord-blood derived mesenchymal stem cells (hUCB-MSCs) have been proposed to secrete a paracrine factor called soluble intracellular adhesion molecule-1 (slCAM-1) which stimulated neighboring microglia cells to overexpress neprilysin, an Aβ degrading enzyme, and subsequently augmented Aβ removal (Kim et al., 2012). Other than parenchymal administration, amyloid removal was also observed from 5x Familial Alzheimer's disease (5xFAD) mouse models, when murine BM-MSCs were injected into the lateral ventricle (Matchynski-Franks et al., 2016) or following intravenous (IV) injections of human MSCs in

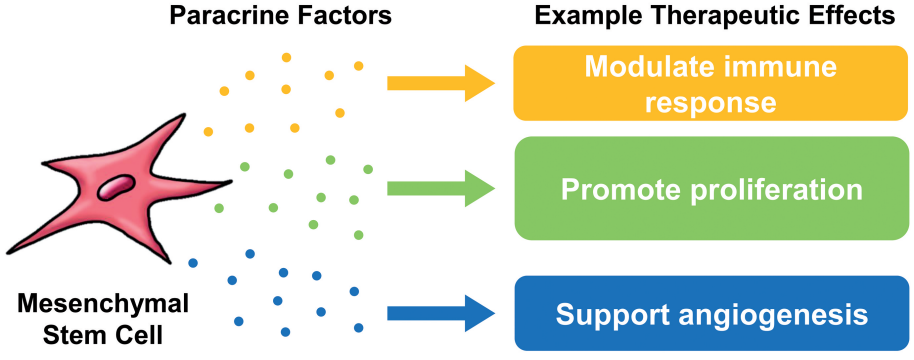

Fig. 1. The mechanism of action of mesenchymal stem cells. Originally introduced by Dr. Arnold Caplan, MSCs initially respond to injury by secreting trophic or paracrine factors (illustrated as yellow, green, and blue circles) into the host environment. These factors serve various immunomodulatory and regenerative functions.

an APP/PS1 mouse model (Harach et al., 2017). One study reported that modifying MSCs to overexpress VEGF, an angiogenic factor, also promoted amyloid clearance in a double transgenic AD mouse model (2xTg) (Garcia et al., 2014). Many studies have also suggested that MSC-induced reduction of amyloid deposits have resulted in improving the memory deficits of transgenic AD mouse models (Lee et al., 2010b; Duncan and Valenzuela, 2017).

Several groups have reported on the immunomodulatory effects exerted by MSCs transplanted into transgenic AD mouse models. MSCs attenuated levels of pro-inflammatory cytokines such as tumor necrophic factor alpha (TNF-α) and interleukin 1 beta (IL-1β), and increased the expressions of anti-inflammatory cytokines such as interleukin 4 (IL-4), tumor necrosis factor beta

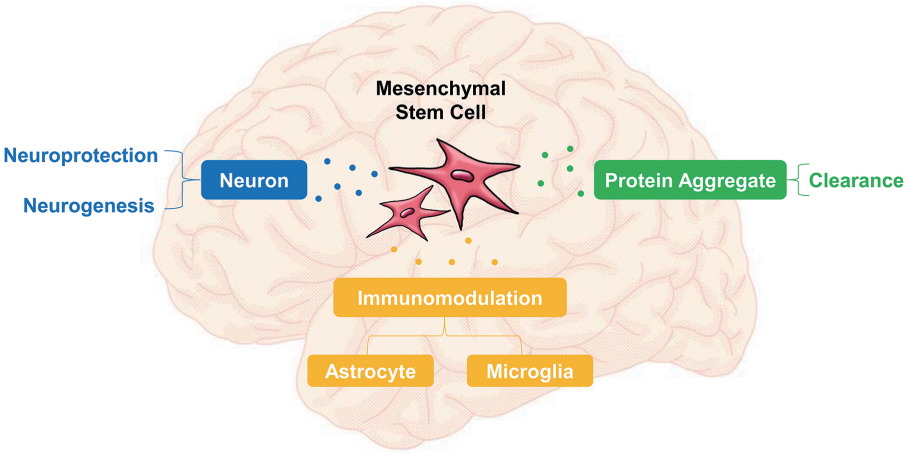

Fig. 2. Therapeutic action of MSCs in neurodegenerative diseases. The background and etiologies of the following neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and Huntington's disease are complex. MSCs confront these complicated diseases by secreting a variety of paracrine factors. Several MSC-based therapeutic effects that can be noted from neurodegenerative diseases include immunomodulation (expressions of inflammatory cells such as astrocyte and microglia are regulated), neuroprotection / neurogenesis, and protein clearance (i.e. Aβ proteins in Alzheimer's disease).

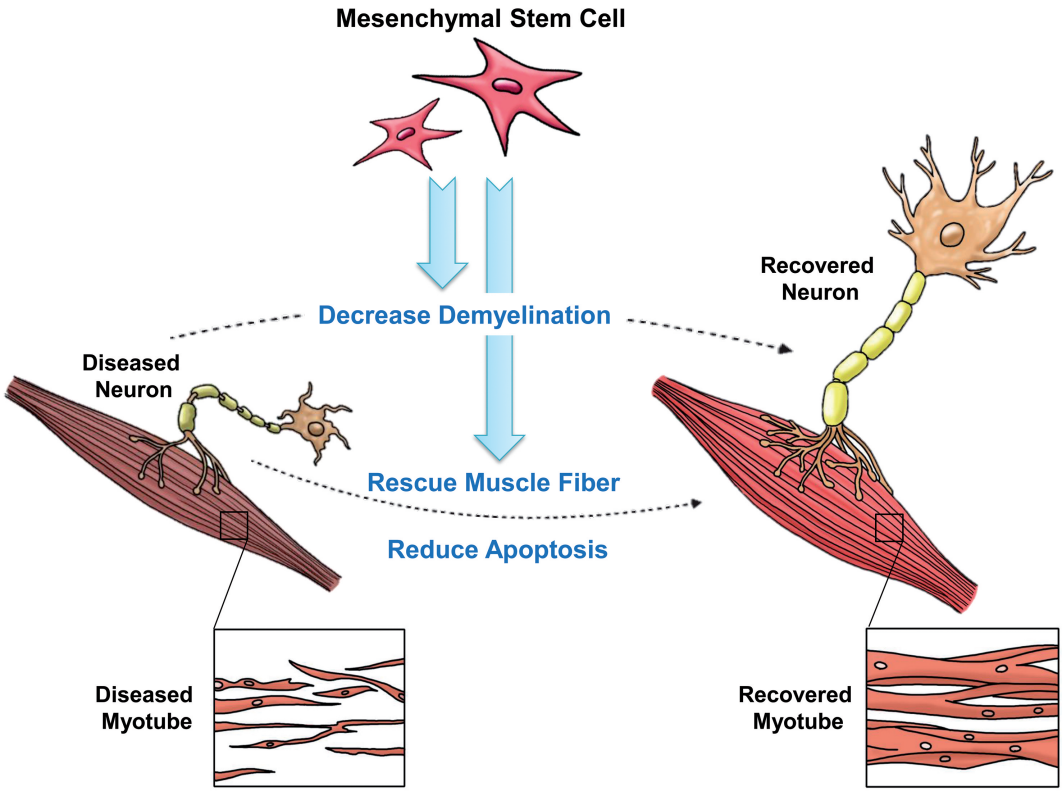

Fig. 3. Therapeutic action of MSCs in muscle diseases. Several pathological features that can be displayed from muscle diseases such as Duchenne muscular dystrophy, myopathy, and multiple sclerosis include demyelination and diseased muscle fibers which subsequently affect the formation and survival of myotubes. MSCs can serve regenerative purposes by decreasing demyelination, rescuing muscle fibers and reducing apoptosis.

(TNF-β), and IL-10 (Lee et al., 2012a; Duncan and Valenzuela, 2017). Levels of activated microglia were also increased, which could have contributed to the phagocytosis of amyloid plaques. It has been reported that soluble C-C motif chemokine ligand 5 (CCL5) secreted by bone-marrow derived MSCs drive the recruitment of activated microglia when transplanted into the brains of transgenic AD mice (Lee et al., 2012b).

MSCs are capable of inducing a wide range of neuroprotective effects. Human umbilical cord-blood derived mesenchymal stem cells (hUCB-MSCs) repeatedly delivered to the brains of the APP/PS1 mouse model via the cisterna magna route, secreted a paracrine factor called Growth differentiation factor-15 (GDF-15), which promoted both hippocampal neurogenesis and synaptogenesis (Kim et al., 2015a). Other than neurogenesis, elevated levels of prostaglandin EP2 receptor (PTGER2), which has been reported for its neuroprotective effects, were also identified from the hippocampi of transgenic AD mice that received MSC administrations (Naaldijk et al., 2017). Several studies have demonstrated ability of MSCs to counteract the toxicity effects induced by amyloid proteins on neuronal cells. Based on an *in vitro* study, co-culturing hUCB-MSCs with Aβ42 protein treated neuronal cells, aroused the secretion of Galectin-3 (GAL-3) which sequentially promoted the survival of neuronal cells and thus demonstrated the ability of MSCs to counteract the toxicity effects induced by amyloid proteins (Kim et al., 2010). Enhancement of proteasome activity was brought forth following co-culture of SH-SY5Y neuroblastoma cells with WJ-MSCs and also hippocampal injections of WJ-MSCs into the 5xFAD mouse brain (Lee et al., 2017). The proteasome activity has been reported to be altered in AD (Oddo, 2008). Secretion of a neuropeptide called Agouti related peptide (AgRP) upregulated the proteasome activity and thus mediated the clearance of ubiquitin-conjugated proteins (Lee et al., 2017).

Parkinson's disease

Another chronic neurodegenerative disease that strongly affects the aging population is Parkinson's disease (PD). A pathological hallmark of PD is Lewy bodies or intracytoplasmic inclusions, and their formation is thought to be triggered by a mutation of the α-synuclein protein (Gundersen, 2010). A major characteristic of PD is the loss in number of dopaminergic (DA) neurons which are normally found in the substantia nigra of the brain (Gugliandolo et al., 2017). As a result, dopamine levels are attenuated in the striatum. The mechanism underlying this loss is not yet completely understood. Like AD, current treatment options have not been able to prohibit or reverse the loss of DA neurons (Glavaski-Joksimovic and Bohn, 2013). Current treatments involve the use of levodopa as a replacement for dopamine; however, side effects such as dyskinesia arise following long term use (Encarnacion and Hauser, 2008).

The trophic factors secreted by MSCs serve a meaningful role in boosting the survival of dopaminergic neurons. For instance, BM-MSCs have been reported to secrete factors such as glial cell line-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF), all cytokines known for their neuroprotective roles (Hyman et al., 1991; Wang et al., 2008; Budni et al., 2015). This is suggested to have supported the survival of dopaminergic neurons in both cell and animal PD models (Baraniak and McDevitt, 2010). Like in AD, where MSCs were reported to counter the toxic effects induced by Aβ, BM-MSCs were demonstrated to shield mouse derived neural stem cells from the toxicity induced by 6-hydroxydopamine (6-OHDA) in an *in vitro* co-culture study (Cova et al., 2012). One of the classical animal PD models is generated by intracerebral transplantation of 6-OHDA which subsequently destroys the DA neurons in the SVZ (Simola et al., 2007). When MSCs were transplanted via routes such as the intrastriatal and IV routes into the brains of 6-OHDA induced PD models, endogenous neurogenesis was enhanced in the SVZ (Cova et al., 2010; Gugliandolo et al., 2017). Such neuroprotective effects would have been promoted by the secretion of trophic factors such as BDNF, GDNF, and neurotrophin-3 (NT-3) by MSCs (Drago et al., 2013).

It has been reported that inflammation contributes to the neurodegeneration of PD. Specifically, activated microglia is suggested to have an association with the loss of DA neurons (Ouchi et al., 2005; Kim et al., 2009). Along with reactive microglia, levels of proinflammatory cytokines such as interferon-gamma (IFN-γ), TNFα and IL-1β have been identified from PD models and the postmortem brain (Nagatsu et al., 2000; Glavaski-Joksimovic and Bohn, 2013). Not only in 6-OHDA induced PD models, but also in other animal PD models that involve the use of neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone, signs of inflammation were exhibited from the death of DA neurons (Lee and Park, 2009). Considering the immunomodulatory properties of MSCs, it is highly possible that transplanted MSCs will be capable of ameliorating the inflammatory responses in PD. Administrations of human MSCs into PD animal models have been reported to attenuate the activation of microglial cells (Park et al., 2008). In another study, following IV administration of mouse BM-MSCs into a MPTP-induced PD model, not only was a decrease in the activation of microglial cells evident, but DA neurons were also protected from the toxicity of the neurotoxin (Chao et al., 2009). The multiple effects exerted by MSCs seemed to collectively rescue the behavior of PD animal models. For instance, in a rotenone-induced Sprague Dawley (SD) rat PD model, when MSCs of human origin were injected into the corpus striatum,

enhancement of behavioral activity was observed by improved apomorphine-induced rotations (Xiong et al., 2010). In another study, injections of human umbilical cord derived mesenchymal stem cells or BM-MSCs into the substantia nigra of 6-OHDA rat PD models significantly reduced the number of amorphine-induced rotations starting at 6 weeks following transplantation (Shetty et al., 2013). A MPTP mouse model injected with BM-MSCs into the striatum exhibited improvement in the rotarod test when compared to the performance of the sham group (Li et al., 2001).

Huntington's disease

Huntington's disease (HD) is an autosomal-dominant, inherited neurodegenerative disease. It involves the expansion of the DNA sequence, cytosine-adenine, guanine, or CAG in exon 1 of the Huntingtin (HTT) gene. Cleavage of this abnormal expansion generates fragments which are reported to misfold into aggregates or inclusion bodies in the nuclei or neurons (Rubinsztein and Carmichael, 2003). Similar to Parkinson's disease, Huntington's disease, is characterized by a loss of neurons specifically of GABAergic medium spiny neurons which are generally localized in the striatum. There are both chemical and transgenic animal models of Huntington's disease. Common chemical models include the use of quinolinic acid (QA) and 3-nitropropionic acid (3-NP) which are capable of inducing HD-like symptoms. Transgenic animal models are created by repeating the CAG sequence in exon 1 of the HTT gene. Examples of these models include R6/2, R6/2-J2, and N1T1-82Q2 (Kerkis et al., 2015).

Although efforts have been made to replace the damaged spiny neurons by transplantation of human fetal striatal tissue, the overall clinical benefit was insignificant (Barker et al., 2013). It has also been reported that expressions of the growth factor, BDNF, which plays a significant role in neuronal growth and survival, are attenuated in the striatum of HD patients (Xie et al., 2010). MSCs seem to hold an attractive position in HD therapy because unlike human fetal striatal tissue, MSCs are readily accessible with limited ethical restraints. Furthermore, MSCs are known to secrete growth factors such as BDNF, indicating their potential to promote neuronal growth. For instance, a partial but positive expression of BDNF was detected from adipose derived stem cells transplanted into the striatum of a QA mouse model (Lee et al., 2009)

When human BM-MSCs were injected into the striatum of QA-lesioned mice, a reduction in striatal degeneration was observed by induction of neural proliferation and decrease in cell apoptosis. Rotarod performance was also improved following MSC transplantation (Lin et al., 2011). Moreover, human adipose stem cells delivered into each bilateral striata of R6/2 mice brought forth neuroprotective effects such as reduced loss of striatal neurons (Lee et al., 2009). Stem cell administration also reduced the formation of ubiquitin-positive aggregates which can be commonly identified from R6/2 mice where the ubiquitin proteasome system or UPS is impaired (Lee et al., 2009).

MSCs in the treatment of muscle diseases

Duchenne muscular dystrophy and myopathy

The regenerative properties of MSCs mean they hold a promising role in the treatment of muscle diseases such as Duchenne muscular dystrophy (DMD). DMD is characterized by a mutation of the dystrophin gene which is located in the outer membrane of muscle fibers. Muscles deficient of this gene are more prone to damage (Sienkiewicz et al., 2015). Regeneration of damaged muscle fibers is, however, hindered by the impairment of resident muscle satellite cells (Markert et al., 2009). Inflammation is a key player in DMD. For example, it has been reported that M1-like macrophages, known for their cytotoxic and anti-angiogenic properties, infiltrate the dystrophin-deficient muscle (Ichim et al., 2010). Blocking the IKK/NF-kappa B signaling pathway is suggested to be an effective method to hinder the progression of DMD (Acharyya et al., 2007).

MSCs have been demonstrated to hold a promising role in restoring the muscle defects of DMD and myopathy models. According to a past study, intramuscular injection of adult human synovial membrane-derived MSCs (hSM-MSCs) in an *mdx* DMD mouse model rescued the expression of dystrophin levels in the muscle fibers and also reduced the centralization of nuclei in the muscle fibers, which is a pathological marker that can be identified from DMD (De Bari et al., 2003; Folker and Baylies, 2013). The *mdx* mouse is a widely used DMD model that is dystrophin-deficient due to the mutation of the *mdx* gene (McGreevy et al., 2015). Additionally, hSM-MSC transplantation partially restored the RNA expression of the mechano growth factor (MGF) which has been reported to be defective in dystrophic *mdx* muscles (Goldspink, 1999; De Bari et al., 2003). The differentiation potential of MSCs has also been utilized as a treatment option for DMD. For instance, Fetal liver kinase one positive (Flk-1+) adipose tissue derived human MSCs administered directly into the cardiotoxin-treated tibialis anterior muscle of an *mdx* mouse model not only differentiated into myofibers but also rescued the expression of dystrophin levels (Liu et al., 2007).

In another study, secretion of chemokine (C motif) ligand 1 (XCL1) by WJ-MSCs significantly reduced the apoptosis of serum deprived or lovastatin-treated/exposed in both mouse skeletal myoblast cell lines (C2C12) and differentiated myotubes (Kwon et al., 2016). Furthermore, XCL1 rescued the disrupted muscle tissues of a zebrafish myopathy model. Transplantation of BM-MSCs also improved the regeneration of damaged muscle fibers of a skeletal muscle atrophy rat

model that was induced by repeated local administrations of botulinum toxin-A (BTX-A) (Shehata et al., 2017).

MSC transplantations have also been conducted using large animal DMD models. Recently, human adipose tissue-derived MSCs were injected into the cephalic vein of Golden Retriever Muscular Dystrophy (GRMD) models (Pelatti et al., 2016). These GRMD dogs received multiple injections of MSCs. The safety of the procedure was confirmed and based on a follow-up that was performed up to 7 years, negative side effects were not noted from the repeated MSC administrations.

Multiple sclerosis

Multiple sclerosis (MS) is a disease that is predominantly characterized by demyelination and chronic inflammation of the central nervous system (Dulamea, 2015). To this date, no effective treatments are available for MS. The underlying pathology of MS is complicated but several pathological features of MS include demyelination and inflammation as mentioned previously and also axonal damage and gliosis (Constantinescu et al., 2011). Clinically, a relapsing-remitting (RR) pattern can be identified from MS patients. Amelioration in pathology was observed upon IV administration of murine BM-MSCs into experimental autoimmune encephalomyelitis (EAE) mice, a commonly used MS mouse model (Zappia et al., 2005). Specifically, reduced demyelination and inflammatory infiltration were detected following MSC administration. Amelioration of disease severity was also noted when MSCs were injected at earlier stages of EAE. Another group also reported on the beneficial effects, including reduction of axonal loss, gained following IV administration of murine, enhanced green fluorescent protein (eGFP)-transfected BM-MSCs into an EAE mouse model (Gerdoni et al., 2007). MSCs were also reported to inhibit T and B cell responses. Furthermore, the group did not support the idea of MSCs undergoing transdifferentiation *in vivo* because neuronal cells expressing green fluorescence were not detected from the brain parenchyma of the mice. Taken together, it was suggested that MSCs exert their therapeutic benefits by interfering with the autoimmune attack on myelin instead of by rescuing damaged neurons and oligodendrocytes. Another study proposed that IV administration of MSCs alleviates the oxidative stress generated by EAE as well as reducing the expressions of the genes, Poly(ADP-ribose) polymerase-1 (PARP1) and p53, which are genes well known to induce apoptosis (Lanza et al., 2009).

According to some groups that do not suggest that MSCs will undergo transdifferentiation, secretion of trophic factors is a highly possible way for MSCs to exert regenerative effects onto the neuronal environment. For instance, when human BM-MSCs were IV-injected into EAE mice, not only was demyelination and inflammatory cell infiltration reduced but oligodendrocyte proliferation was enhanced (Zhang et al., 2005). Such improvement can influence the repair of myelin. Furthermore, while the original, cellular source of BDNF secretion was not identified, mice injected with human BM-MSCs exhibited higher numbers of BDNF-positive neuronal cells in comparison to that of PBS injected mice. Furthermore, there is a report that after cuprizone induced demyelination, oligodendrocyte progenitor cell proliferation can be prevented due to low levels of BDNF (Tsiperson et al., 2015). Other groups, however, support the possibility of MSCs differentiating into neurons *in vivo*. Although not observed from an EAE mouse model, murine BM-MSCs injected via the intracerebroventricular route into the brains of neonatal mice mimicked the behavior of neural progenitor cells and also possibly differentiated into astrocytes and neurons (Kopen et al., 1999).

Conclusions

The multifaceted aspects of MSCs make them attractive candidates to serve as novel therapeutic agents for incurable neurodegenerative and muscle diseases where the underlying pathologies are wide and complex. Such properties increase their potential to be applied broadly in a wide range of diseases including rare diseases such as Charcot-Marie-Tooth and Niemann-Pick type C diseases. One of the major pathological hallmarks of Charcot-Marie-Tooth is demyelination. As touched upon in this review, it is highly possible that MSCs will support remyelination and play a therapeutic role if applied to the treatment of this genetic disease. Although further extensive research is required, there has been a report that administrations of BM-MSCs ameliorated the loss of Purkinje neurons in a mouse model Niemann-Pick type C disease (Lee et al., 2010a), thus, reinforcing the potential application of MSCs in the treatment of Niemann-Pick type C disease.

The safety of MSCs has been confirmed from various clinical trials aimed at treating diseases such as Alzheimer's disease (Kim et al., 2015b; Hunsberger et al., 2016) and multiple sclerosis (Karussis et al., 2010). Along with safety, some groups have proposed that MSC transplantation in diseases such as MS and amyotrophic lateral sclerosis (ALS) contributed towards neurological improvement (Squillaro et al., 2016). It is highly possible that in order to observe therapeutic benefits, MSCs must be administered at earlier time points, such as the mild cognitive impairment stage in AD, before reaching the chronic stages of the disease. For instance, it was reported that MSC transplantation at earlier stages of the disease improved the clinical symptoms of EAE mice (Payne et al., 2012). Efficacy can also be possibly enhanced if repeated injections of MSCs were also performed (Kim et al., 2015b; Oh et al., 2015). Further study is warranted to provide conclusive evidence to support the long-term safety and also clinical efficacy of MSC transplantation in both neurodegenerative and muscle diseases.

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References

Acharyya S., Villalta S.A., Bakkar N., Bupha-Intr T., Janssen P.M., Carathers M., Li Z.W., Beg A.A., Ghosh S., Sahenk Z., Weinstein M., Gardner K.L., Rafael-Fortney J.A., Karin M., Tidball J.G., Baldwin A.S. and Guttridge D.C. (2007). Interplay of Ikk/Nf-Kappab signaling in macrophages and myofibers promotes muscle degeneration in Duchenne muscular dystrophy. J. Clin. Invest. 117, 889-901.

Ankrum J.A., Ong J.F. and Karp J.M. (2014). Mesenchymal stem cells: Immune evasive, not immune privileged. Nat. Biotechnol. 32, 252-260.

Baraniak P.R. and McDevitt T.C. (2010). Stem cell paracrine actions and tissue regeneration. Regen. Med. 5, 121-143.

Barker R.A., Mason S.L., Harrower T.P., Swain R.A., Ho A.K., Sahakian B.J., Mathur R., Elneil S., Thornton S., Hurrelbrink C., Armstrong R.J., Tyers P., Smith E., Carpenter A., Piccini P., Tai Y.F., Brooks D.J., Pavese N., Watts C., Pickard J.D., Rosser A.E., Dunnett S.B. and collaboration N.-U. (2013). The long-term safety and efficacy of bilateral transplantation of human fetal striatal tissue in patients with mild to moderate Huntington's disease. J. Neurol. Neurosurg. Psychiatry 84, 657-665.

Block G.J., Ohkouchi S., Fung F., Frenkel J., Gregory C., Pochampally R., DiMattia G., Sullivan D.E. and Prockop D.J. (2009). Multipotent stromal cells are activated to reduce apoptosis in part by upregulation and secretion of stanniocalcin-1. Stem Cells 27, 670-681.

Budni J., Bellettini-Santos T., Mina F., Garcez M.L. and Zugno A.I. (2015). The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease. Aging Dis. 6, 331-341.

Caplan A.I. (2010). What's in a name? Tissue Eng. Part A 16, 2415-2417.

Caplan A.I. (2017a). Mesenchymal stem cells: Time to change the name! Stem Cells Transl. Med. 6, 1445-1451.

Caplan A.I. (2017b). New MSC: MSCs as pericytes are sentinels and gatekeepers. J. Orthop. Res. 35, 1151-1159.

Caplan A.I. and Correa D. (2011). The MSC: An injury drugstore. Cell Stem Cell 9, 11-15.

Caplan A.I. and Dennis J.E. (2006). Mesenchymal stem cells as trophic mediators. J. Cell Biochem. 98, 1076-1084.

Chao Y.X., He B.P. and Tay S.S. (2009). Mesenchymal stem cell transplantation attenuates blood brain barrier damage and neuroinflammation and protects dopaminergic neurons against MPTP toxicity in the substantia nigra in a model of Parkinson's disease. J. Neuroimmunol. 216, 39-50.

Chin-Chan M., Navarro-Yepes J. and Quintanilla-Vega B. (2015). Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Front. Cell Neurosci. 9, 124.

Constantinescu C.S., Farooqi N., O'Brien K. and Gran B. (2011). Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br. J. Pharmacol. 164, 1079-1106.

Cova L., Armentero M.T., Zennaro E., Calzarossa C., Bossolasco P., Busca G., Lambertenghi Deliliers G., Polli E., Nappi G., Silani V. and Blandini F. (2010). Multiple neurogenic and neurorescue effects of human mesenchymal stem cell after transplantation in an experimental model of Parkinson's disease. Brain Res. 1311, 12-27.

Cova L., Bossolasco P., Armentero M.T., Diana V., Zennaro E., Mellone M., Calzarossa C., Cerri S., Deliliers G.L., Polli E., Blandini F. and Silani V. (2012). Neuroprotective effects of human mesenchymal stem cells on neural cultures exposed to 6-hydroxydopamine: implications for reparative therapy in Parkinson's disease. Apoptosis 17, 289-304.

De Bari C., Dell'Accio F., Vandenabeele F., Vermeesch J.R., Raymackers J.M. and Luyten F.P. (2003). Skeletal muscle repair by adult human mesenchymal stem cells from synovial membrane. J. Cell Biol. 160, 909-918.

Deconinck N. and Dan B. (2007). Pathophysiology of duchenne muscular dystrophy: Current hypotheses. Pediatr. Neurol. 36, 1-7.

Dominici M., Le Blanc K., Mueller I., Slaper-Cortenbach I., Marini F., Krause D., Deans R., Keating A., Prockop D. and Horwitz E. (2006). Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy Position Statement. Cytotherapy 8, 315-317.

Drago D., Cossetti C., Iraci N., Gaude E., Musco G., Bachi A. and Pluchino S. (2013). The stem cell secretome and its role in brain repair. Biochimie 95, 2271-2285.

Dulamea A. (2015). Mesenchymal stem cells in multiple sclerosis - Translation to clinical trials. J. Med. Life 8, 24-27.

Duncan T. and Valenzuela M. (2017). Alzheimer's disease, dementia, and stem cell therapy. Stem Cell Res. Ther. 8, 111.

Encarnacion E.V. and Hauser R.A. (2008). Levodopa-induced dyskinesias in Parkinson's disease: Etiology, impact on quality of life, and treatments. Eur. Neurol. 60, 57-66.

Folker E.S. and Baylies M.K. (2013). Nuclear positioning in muscle development and disease. Front. Physiol 4, 363.

Garcia K.O., Ornellas F.L., Martin P.K., Patti C.L., Mello L.E., Frussa-Filho R., Han S.W. and Longo B.M. (2014). Therapeutic effects of the transplantation of VEGF overexpressing bone marrow mesenchymal stem cells in the hippocampus of murine model of Alzheimer's disease. Front. Aging Neurosci. 6, 30.

Gerdoni E., Gallo B., Casazza S., Musio S., Bonanni I., Pedemonte E., Mantegazza R., Frassoni F., Mancardi G., Pedotti R. and Uccelli A. (2007). Mesenchymal stem cells effectively modulate pathogenic immune response in experimental autoimmune encephalomyelitis. Ann. Neurol. 61, 219-227.

Ghannam S., Bouffi C., Djouad F., Jorgensen C. and Noel D. (2010). Immunosuppression by mesenchymal stem cells: Mechanisms and clinical applications. Stem Cell Res. Ther. 1, 2.

Giacobini E. and Gold G. (2013). Alzheimer disease therapy--Moving from amyloid-beta to Tau. Nat. Rev. Neurol. 9, 677-686.

Gitler A.D., Dhillon P. and Shorter J. (2017). Neurodegenerative disease: Models, mechanisms, and a new hope. Dis. Model Mech. 10, 499-502.

Glavaski-Joksimovic A. and Bohn M.C. (2013). Mesenchymal stem cells

and neuroregeneration in Parkinson's disease. Exp. Neurol. 247, 25-38.

Gold M. (2017). Phase II clinical trials of anti-amyloid β antibodies: When is enough, enough? Alzheimer's Dement. 3, 402-409.

Goldspink G. (1999). Changes in muscle mass and phenotype and the expression of autocrine and systemic growth factors by muscle in response to stretch and overload. J. Anat. 194 (Pt 3), 323-334.

Gugliandolo A., Bramanti P. and Mazzon E. (2017). Mesenchymal stem cell therapy in Parkinson's disease animal models. Curr Res. Transl. Med. 65, 51-60.

Gundersen V. (2010). Protein aggregation in Parkinson's disease. Acta Neurol. Scand Suppl, 82-87.

Harach T., Jammes F., Muller C., Duthilleul N., Cheatham V., Zufferey V., Cheatham D., Lukasheva Y.A., Lasser T. and Bolmont T. (2017). Administrations of human adult ischemia-tolerant mesenchymal stem cells and factors reduce amyloid beta pathology in a mouse model of Alzheimer's disease. Neurobiol. Aging 51, 83-96.

Huang G.T., Gronthos S. and Shi S. (2009). Mesenchymal stem cells derived from dental tissues vs. those from other sources: Their biology and role in regenerative medicine. J. Dent. Res. 88, 792-806.

Hunsberger J.G., Rao M., Kurtzberg J., Bulte J.W.M., Atala A., LaFerla F.M., Greely H.T., Sawa A., Gandy S., Schneider L.S. and Doraiswamy P.M. (2016). Accelerating stem cell trials for Alzheimer's disease. Lancet Neurol. 15, 219-230.

Hyman C., Hofer M., Barde Y.A., Juhasz M., Yancopoulos G.D., Squinto S.P. and Lindsay R.M. (1991). BDNF is a neurotrophic factor for dopaminergic neurons of the substantia nigra. Nature 350, 230-232.

Ichim T.E., Alexandrescu D.T., Solano F., Lara F., Campion Rde N., Paris E., Woods E.J., Murphy M.P., Dasanu C.A., Patel A.N., Marleau A.M., Leal A. and Riordan N.H. (2010). Mesenchymal stem cells as anti-inflammatories: Implications for treatment of Duchenne muscular dystrophy. Cell Immunol. 260, 75-82.

Johnson I.P. (2015). Age-related neurodegenerative disease research needs aging models. Front. Aging Neurosci. 7, 168.

Karussis D., Karageorgiou C., Vaknin-Dembinsky A., Gowda-Kurkalli B., Gomori J.M., Kassis I., Bulte J.W., Petrou P., Ben-Hur T., Abramsky O. and Slavin S. (2010). Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis. Arch. Neurol. 67, 1187-1194.

Kerkis I., Haddad M.S., Valverde C.W. and Glosman S. (2015). Neural and mesenchymal stem cells in animal models of Huntington's disease: Past experiences and future challenges. Stem Cell. Res. Ther. 6, 232.

Kim D.H., Lee D., Chang E.H., Kim J.H., Hwang J.W., Kim J.Y., Kyung J.W., Kim S.H., Oh J.S., Shim S.M., Na D.L., Oh W. and Chang J.W. (2015a). GDF-15 secreted from human umbilical cord blood mesenchymal stem cells delivered through the cerebrospinal fluid promotes hippocampal neurogenesis and synaptic activity in an Alzheimer's disease model. Stem Cells Dev. 24, 2378-2390.

Kim H., Seo S., Chang J., Lee J., Kim C., Chin J., Choi S., Kwon H., Yun H., Lee J., Kim S., Choe Y., Lee K. and Na D. (2015b). Stereotactic brain injection of human umbilical cord blood mesenchymal stem cells in patients with Alzheimer's disease dementia: A phase 1 clinical trial. Alzheimers Dement. 1, 95-102.

Kim J.Y., Kim D.H., Kim D.S., Kim J.H., Jeong S.Y., Jeon H.B., Lee E.H., Yang Y.S., Oh W. and Chang J.W. (2010). Galectin-3 secreted by human umbilical cord blood-derived mesenchymal stem cells reduces amyloid-beta42 neurotoxicity *in vitro*. FEBS Lett. 584, 3601-3608.

Kim J.Y., Kim D.H., Kim J.H., Lee D., Jeon H.B., Kwon S.J., Kim S.M., Yoo Y.J., Lee E.H., Choi S.J., Seo S.W., Lee J.I., Na D.L., Yang Y.S., Oh W. and Chang J.W. (2012). Soluble intracellular adhesion molecule-1 secreted by human umbilical cord blood-derived mesenchymal stem cell reduces amyloid-beta plaques. Cell Death Differ 19, 680-691.

Kim Y.J., Park H.J., Lee G., Bang O.Y., Ahn Y.H., Joe E., Kim H.O. and Lee P.H. (2009). Neuroprotective effects of human mesenchymal stem cells on dopaminergic neurons through anti-inflammatory action. Glia 57, 13-23.

Kopen G.C., Prockop D.J. and Phinney D.G. (1999). Marrow stromal cells migrate throughout forebrain and cerebellum, and they differentiate into astrocytes after injection into neonatal mouse brains. Proc. Natl. Acad. Sci. USA 96, 10711-10716.

Kwon S., Ki S.M., Park S.E., Kim M.J., Hyung B., Lee N.K., Shim S., Choi B.O., Na D.L., Lee J.E. and Chang J.W. (2016). Anti-apoptotic effects of human wharton's jelly-derived mesenchymal stem cells on skeletal muscle cells mediated via secretion of XCL1. Mol. Ther. 24, 1550-1560.

Lanza C., Morando S., Voci A., Canesi L., Principato M.C., Serpero L.D., Mancardi G., Uccelli A. and Vergani L. (2009). Neuroprotective mesenchymal stem cells are endowed with a potent antioxidant effect *in vivo*. J. Neurochem. 110, 1674-1684.

Lee P.H. and Park H.J. (2009). Bone marrow-derived mesenchymal stem cell therapy as a candidate disease-modifying strategy in Parkinson's disease and multiple system atrophy. J. Clin. Neurol. 5, 1-10.

Lee S.T., Chu K., Jung K.H., Im W.S., Park J.E., Lim H.C., Won C.H., Shin S.H., Lee S.K., Kim M. and Roh J.K. (2009). Slowed progression in models of Huntington disease by adipose stem cell transplantation. Ann. Neurol. 66, 671-681.

Lee H., Lee J.K., Min W.K., Bae J.H., He X., Schuchman E.H., Bae J.S. and Jin H.K. (2010a). Bone marrow-derived mesenchymal stem cells prevent the loss of Niemann-Pick type C mouse purkinje neurons by correcting sphingolipid metabolism and increasing sphingosine-1-phosphate. Stem Cells 28, 821-831.

Lee J.K., Jin H.K., Endo S., Schuchman E.H., Carter J.E. and Bae J.S. (2010b). Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. Stem Cells 28, 329-343.

Lee H.J., Lee J.K., Lee H., Carter J.E., Chang J.W., Oh W., Yang Y.S., Suh J.G., Lee B.H., Jin H.K. and Bae J.S. (2012a). Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. Neurobiol. Aging 33, 588-602.

Lee J.K., Schuchman E.H., Jin H.K. and Bae J.S. (2012b). Soluble CCL5 derived from bone marrow-derived mesenchymal stem cells and activated by amyloid beta ameliorates Alzheimer's disease in mice by recruiting bone marrow-induced microglia immune responses. Stem Cells 30, 1544-1555.

Lee N.K., Park S.E., Kwon S.J., Shim S., Byeon Y., Kim J.H., Na D.L. and Chang J.W. (2017). Agouti related peptide secreted via human mesenchymal stem cells upregulates proteasome activity in an Alzheimer's disease model. Sci. Rep. 7, 39340.

Lewis C.M. and Suzuki M. (2014). Therapeutic applications of

mesenchymal stem cells for amyotrophic lateral sclerosis. Stem Cell Res. Ther 5, 32.

Li Y., Chen J., Wang L., Zhang L., Lu M. and Chopp M. (2001). Intracerebral transplantation of bone marrow stromal cells in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. Neurosci. Lett. 316, 67-70.

Lin Y.T., Chern Y., Shen C.K., Wen H.L., Chang Y.C., Li H., Cheng T.H. and Hsieh-Li H.M. (2011). Human mesenchymal stem cells prolong survival and ameliorate motor deficit through trophic support in Huntington's disease mouse models. PLoS One 6, e22924.

Liu Y., Yan X., Sun Z., Chen B., Han Q., Li J. and Zhao R.C. (2007). Flk-1+ Adipose-derived mesenchymal stem cells differentiate into skeletal muscle satellite cells and ameliorate muscular dystrophy in Mdx mice. Stem Cells Dev. 16, 695-706.

Lu J.J., Pan W., Hu Y.J. and Wang Y.T. (2012). Multi-target drugs: The trend of drug research and development. PLoS One 7, e40262.

Ma S., Xie N., Li W., Yuan B., Shi Y. and Wang Y. (2014). Immunobiology of mesenchymal stem cells. Cell Death Differ. 21, 216-225.

Markert C.D., Atala A., Cann J.K., Christ G., Furth M., Ambrosio F. and Childers M.K. (2009). Mesenchymal stem cells: Emerging therapy for Duchenne muscular dystrophy. PM R 1, 547-559.

Matchynski-Franks J.J., Pappas C., Rossignol J., Reinke T., Fink K., Crane A., Twite A., Lowrance S.A., Song C. and Dunbar G.L. (2016). Mesenchymal stem cells as treatment for behavioral deficits and neuropathology in the 5xFAD mouse model of Alzheimer's disease. Cell Transplant. 25, 687-703.

McGreevy J.W., Hakim C.H., McIntosh M.A. and Duan D. (2015). Animal models of Duchenne muscular dystrophy: From basic mechanisms to gene therapy. Dis. Model Mech. 8, 195-213.

Naaldijk Y., Jager C., Fabian C., Leovsky C., Bluher A., Rudolph L., Hinze A. and Stolzing A. (2017). Effect of systemic transplantation of bone marrow-derived mesenchymal stem cells on neuropathology markers in APP/PS1 Alzheimer mice. Neuropathol. Appl. Neurobiol. 43, 299-314.

Nagatsu T., Mogi M., Ichinose H. and Togari A. (2000). Cytokines in Parkinson's disease. J. Neural Transm. Suppl., 143-151.

Oddo S. (2008). The ubiquitin-proteasome system in Alzheimer's disease. J. Cell. Mol. Med. 12, 363-373.

Oh K.W., Moon C., Kim H.Y., Oh S.I., Park J., Lee J.H., Chang I.Y., Kim K.S. and Kim S.H. (2015). Phase I trial of repeated intrathecal autologous bone marrow-derived mesenchymal stromal cells in amyotrophic lateral sclerosis. Stem Cells Transl. Med. 4, 590-597.

Ouchi Y., Yoshikawa E., Sekine Y., Futatsubashi M., Kanno T., Ogusu T. and Torizuka T. (2005). Microglial activation and dopamine terminal loss in early Parkinson's disease. Ann. Neurol. 57, 168-175.

Park H.J., Lee P.H., Bang O.Y., Lee G. and Ahn Y.H. (2008). Mesenchymal stem cells therapy exerts neuroprotection in a progressive animal model of Parkinson's disease. J. Neurochem. 107, 141-151.

Payne N.L., Dantanarayana A., Sun G., Moussa L., Caine S., McDonald C., Herszfeld D., Bernard C.C. and Siatskas C. (2012). Early intervention with gene-modified mesenchymal stem cells overexpressing interleukin-4 enhances anti-inflammatory responses and functional recovery in experimental autoimmune demyelination. Cell Adh. Migr. 6, 179-189.

Pelatti M.V., Gomes J.P., Vieira N.M., Cangussu E., Landini V., Andrade T., Sartori M., Petrus L. and Zatz M. (2016). Transplantation of human adipose mesenchymal stem cells in non-immunosuppressed GRMD dogs is a safe procedure. Stem Cell Rev. 12, 448-453.

Qiu C., Kivipelto M. and von Strauss E. (2009). Epidemiology of Alzheimer's disease: Occurrence, determinants, and strategies toward intervention. Dialogues Clin. Neurosci. 11, 111-128.

Reitz C. (2012). Alzheimer's disease and the amyloid cascade hypothesis: A critical review. Int. J. Alzheimers Dis. 2012, 369808.

Rubinsztein D.C. and Carmichael J. (2003). Huntington's disease: Molecular basis of neurodegeneration. Expert Rev. Mol. Med. 5, 1-21.

Selkoe D.J. and Hardy J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol. Med. 8, 595-608.

Serrano-Pozo A., Frosch M.P., Masliah E. and Hyman B.T. (2011). Neuropathological alterations in Alzheimer disease. Cold Spring Harb. Perspect. Med. 1, a006189.

Shehata A.S., Al-Ghonemy N.M., Ahmed S.M. and Mohamed S.R. (2017). Effect of mesenchymal stem cells on induced skeletal muscle chemodenervation atrophy in adult male albino rats. Int J. Biochem Cell Biol. 85, 135-148.

Shetty P., Thakur A.M. and Viswanathan C. (2013). Dopaminergic cells, derived from a high efficiency differentiation protocol from umbilical cord derived mesenchymal stem cells, alleviate symptoms in a Parkinson's disease rodent model. Cell Biol. Int. 37, 167-180.

Shin T.H., Kim H.S., Choi S.W. and Kang K.S. (2017). Mesenchymal stem cell therapy for inflammatory skin diseases: Clinical potential and mode of action. Int J. Mol. Sci. 18, 244.

Sienkiewicz D., Kulak W., Okurowska-Zawada B., Paszko-Patej G. and Kawnik K. (2015). Duchenne muscular dystrophy: Current cell therapies. Ther. Adv. Neurol. Disord. 8, 166-177.

Simola N., Morelli M. and Carta A.R. (2007). The 6-hydroxydopamine model of Parkinson's disease. Neurotox. Res. 11, 151-167.

Squillaro T., Peluso G. and Galderisi U. (2016). Clinical trials with mesenchymal stem cells: An update. Cell Transplant. 25, 829-848.

Stephenson D., Perry D., Bens C., Bain L.J., Berry D., Krams M., Sperling R., Dilts D., Luthman J., Hanna D., McKew J., Temple R., Fields F.O., Salloway S. and Katz R. (2015). Charting a path toward combination therapy for Alzheimer's disease. Expert Rev. Neurother. 15, 107-113.

Tsiperson V., Huang Y., Bagayogo I., Song Y., VonDran M.W., DiCicco-Bloom E. and Dreyfus C.F. (2015). Brain-derived neurotrophic factor deficiency restricts proliferation of oligodendrocyte progenitors following cuprizone-induced demyelination. ASN Neuro 7.

Turgeman G. (2015). The therapeutic potential of mesenchymal stem cells in Alzheimer's disease: Converging mechanisms. Neural Regen. Res. 10, 698-699.

Wang T.H., Feng Z.T., Wei P., Li H., Shi Z.J. and Li L.Y. (2008). Effects of PCDNA3-beta-NGF gene-modified BMSC on the rat model of Parkinson's disease. J. Mol. Neurosci. 35, 161-169.

Xie Y., Hayden M.R. and Xu B. (2010). BDNF overexpression in the forebrain rescues Huntington's disease phenotypes in Yac128 mice. J. Neurosci. 30, 14708-14718.

Xiong N., Cao X., Zhang Z., Huang J., Chen C., Zhang Z., Jia M., Xiong J., Liang Z., Sun S., Lin Z. and Wang T. (2010). Long-term efficacy and safety of human umbilical cord mesenchymal stromal cells in Rotenone-induced hemiparkinsonian rats. Biol. Blood Marrow Transplant. 16, 1519-1529.

Zappia E., Casazza S., Pedemonte E., Benvenuto F., Bonanni I., Gerdoni E., Giunti D., Ceravolo A., Cazzanti F., Frassoni F., Mancardi G. and Uccelli A. (2005). Mesenchymal stem cells

ameliorate experimental autoimmune encephalomyelitis inducing T-cell anergy. Blood 106, 1755-1761.

Zhang J., Li Y., Chen J., Cui Y., Lu M., Elias S.B., Mitchell J.B., Hammill L., Vanguri P. and Chopp M. (2005). Human bone marrow stromal cell treatment improves neurological functional recovery in EAE mice. Exp. Neurol. 195, 16-26.

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