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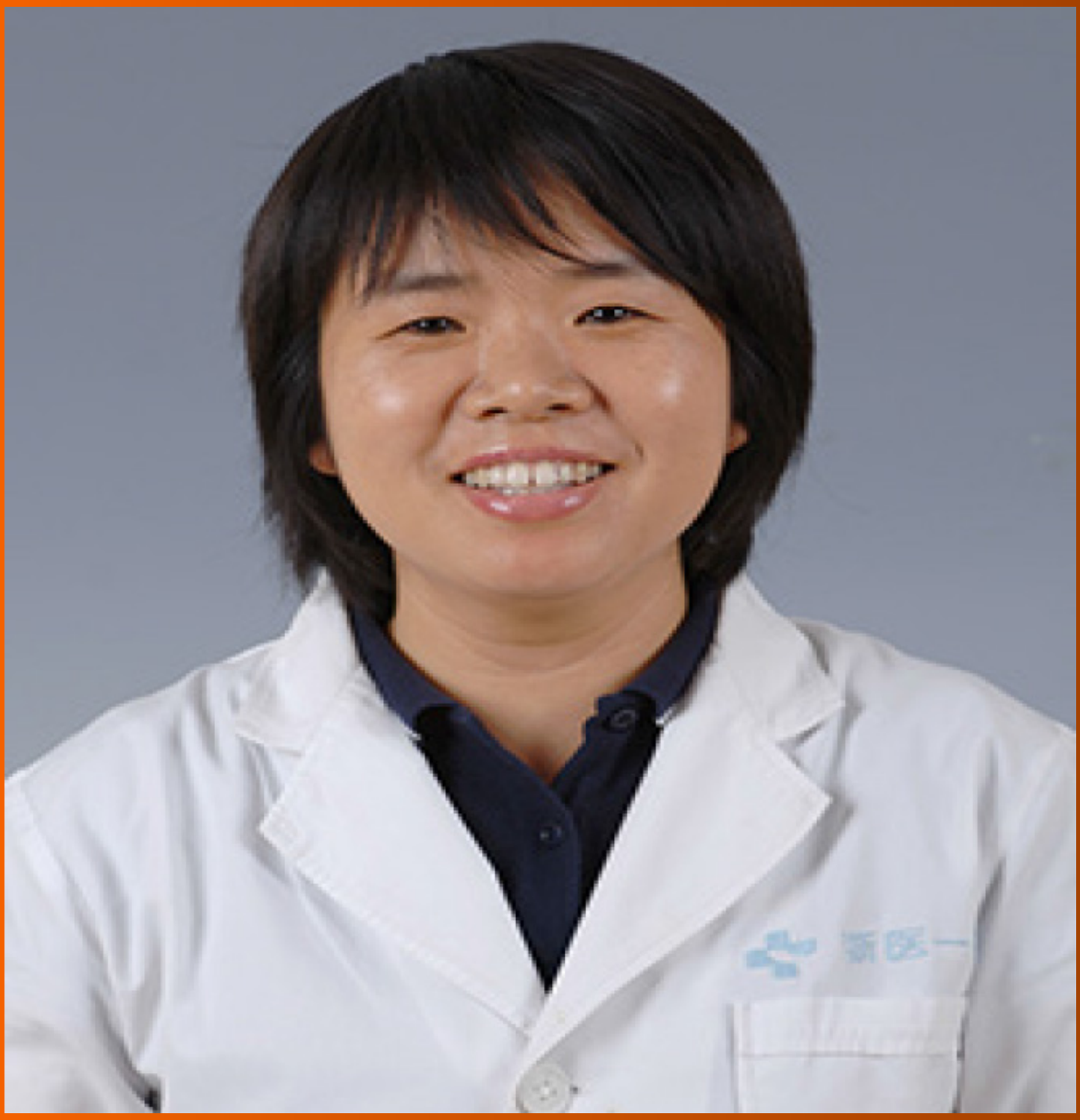

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World Journal of Stem Cells

Contents

Monthly Volume 12 Number 5 May 26, 2020

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Basic Study

SYSTEMATIC REVIEWS

Contents

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Volume 12 Number 5 May 26, 2020

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REVIEW

Advances in treatment of neurodegenerative diseases: Perspectives for combination of stem cells with neurotrophic factors

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Abstract

Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, are a group of incurable neurological disorders, characterized by the chronic progressive loss of different neuronal subtypes. However, despite its increasing prevalence among the ever-increasing aging population, little progress has been made in the coincident immense efforts towards development of therapeutic agents. Research interest has recently turned towards stem cells including stem cells-derived exosomes, neurotrophic factors, and their combination as potential therapeutic agents in neurodegenerative diseases. In this review, we summarize the progress in therapeutic strategies based on stem cells combined with neurotrophic factors and mesenchymal stem cells-derived exosomes for neurodegenerative diseases, with an emphasis on the combination therapy.

Key words: Neurodegenerative diseases; Stem cells; Brain-derived neurotrophic factor; Glial cell line-derived neurotrophic factor; Nerve growth factor; Combination therapy

Core tip: Neurodegenerative diseases are currently incurable and the therapeutic strategies have been disappointing. Stem cells and neurotrophic factors are promising therapeutic agents, with the combination of the two being more attractive. This review focuses on the advances in such combination therapies in the treatment of

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neurodegenerative diseases. The combination of stem cells with neurotrophic factors can not only replenish the target neurons but also provide secreted neurotrophins to improve the microenvironment for nerve repair and regeneration, which might represent a new approach in the treatment of neurodegenerative diseases.

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INTRODUCTION

Neurodegenerative diseases, mainly involving gradual and progressive neuron loss and neuronal function decline, usually lead to cognitive and behavioral dysfunctions and severe life quality impairment of the patients. Currently, there remains a lack of effective therapeutic agents due to the obscure cause of the neuronal death and the impeded early diagnosis of neurodegenerative diseases. Stem cells and neurotrophic factors are promising therapeutic agents with neural differentiation and neuroprotective effects for neurodegenerative diseases[1-3]. Figure 1 illustrates the possible effects of mesenchymal stem cells (MSCs) and neurotrophic factors for each disorder described in this paper.

Stem cells have emerged as one of the most actively researched potential therapeutic tools for a wide range of diseases. They can be divided into pluripotent stem cells and adult stem cells. The former encompasses the embryonic stem cells and induced pluripotent stem cells; the latter includes the neural stem cells (NSCs), hematopoietic stem cells, MSCs, and olfactory ensheathing stem cells. All stem cells have the potentiality of continuous self-renewal, high proliferation, and multidirectional differentiation into various cell types to replace degenerated or dead cells[4]. They also act as neuroprotection and neurodifferentiation promoters by secreting neurotrophic factors (NTFs) and extracellular vesicles (EVs, so called exosomes) containing NTFs. These abilities make stem cells a promising therapeutic choice for neurodegenerative diseases. In particular, MSCs appear to be the most suitable, due to their availability, low immunogenicity, multiple differentiation ability, and secretion of NTFs and exosomes[5-8].

The NTF protein family, mainly consisting of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), neurotrophic factor 3 (NT3) and neurotrophic factor 4 (NT4), are necessary for neuronal development, health and survival, as well as for stem cell proliferation and differentiation into target neurons. Some NTFs are protective to cell survival and neuronal degeneration, which show promise as therapeutic agents for neurodegenerative diseases[2,3]. However, some serious problems, *e.g.*, rapidly degraded NTFs need to be frequently delivered and recombinant NTFs protein cannot pass through the blood-brain barrier (BBB), must be confronted[1,9,10].

Gene transduction by recombinant viral vectors makes it possible for a sustained supply of therapeutic factors after single transfection of target cells. But, the vector systems-associated drawbacks, including toxicity and inflammation, non-relevant cell infection and risk of genome insertional mutagenesis, still prompt alternative therapeutic strategies, such as transplantation of NTF-releasing cells. The effectiveness of this construct has been demonstrated in *in vivo* neuronal disease models, in which cell-delivered BDNF has shown the same or even better neuroprotective effect than recombinant BDNF[11]. MSCs have been considered as the optimal delivery platform for sustained delivery of therapeutically relevant amounts of NTFs to degenerative neuronal structures, because of their secretion of various factors that can reduce inflammation, cell toxicity and cell death, and can enhance neurons connections[12]. Moreover, when compared with MSCs alone, MSCs-NTFs showed better results in several rodent neurodegenerative models[1].

EVs are phospholipid bilayer enveloped spherical particles categorized into exosomes, microvesicles, and apoptotic bodies based on their origin and size. Exosomes are 30–100 nm in diameter and involved in cells communications by transferring genetic material including mRNA and miRNA, proteins, lipids and

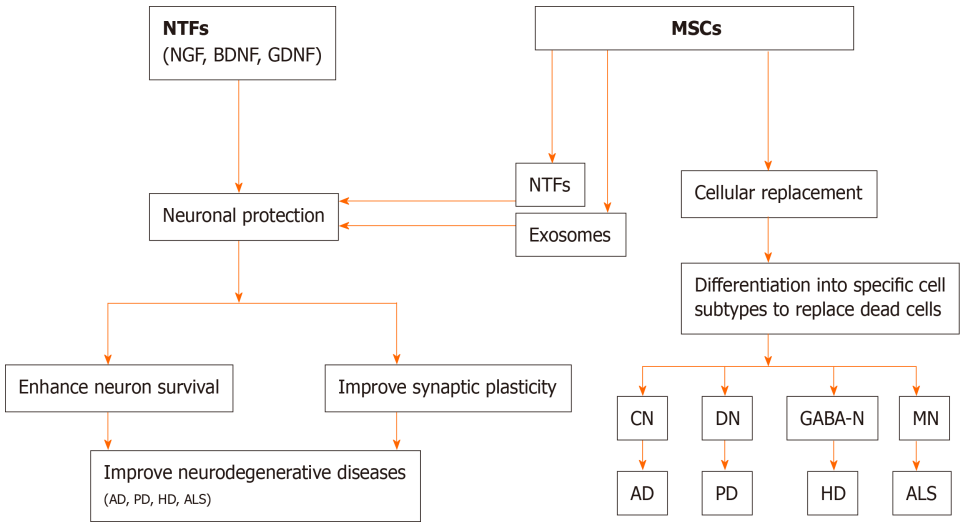

Figure 1 Possible effects of mesenchymal stem cells and neurotrophic factors for Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; BDNF: Brain-derived neurotrophic factor; CN: Cholinergic neurons; DN: Dopamine neurons; GDNF: Glial cell line-derived neurotrophic factor; GABA-N: Striatal GABAergic medium-sized spiny neurons; HD: Huntington's disease; MN: Motor neurons; MSCs: Mesenchymal stem cells; NGF: Nerve growth factor; NTFs: Neurotrophic factors; PD: Parkinson's disease.

membrane receptors[13]. The unability to cross the BBB of most drugs is a great challenge for the treatment of neurodegenerative diseases. Thus, the ability to cross the BBB of exosomes makes it a promising delivery system to transport therapeutical signals or drugs into the brain for neurological diseases like neurodegenerative diseases. Furthermore, sophisticated techniques makes it possible to engineer more precisely targeted exosomes to a desired tissue or region[6,14]. Exosomes can be obtained from different cell types, MSCs can secrete a higher amount of exosomes than other cell types, and MSC-derived exosomes show promising effects in multiple conditions by triggering regeneration responses[15,16]. There is accumulating evidence showing the neurotherapeutic potentiality and successful application of exosomes secreted by various stem cell types, especially MSCs for the treatment of neurodegenerative diseases. MSC-exosomes is currently considered as an alternative non-cell therapy to stem cell therapy. Moreover, the development of genetically modified MSCs-exosomes might provide a new perspective for developing therapeutic strategies for neurodegenerative diseases in the future[6,17].

In summary, stem cells, NTFs and MSC-exosomes are promising therapeutics for neurodegenerative diseases with their own distinctive advantages and disadvantages. The combination therapy might not only have enhanced effect but also play a complementary role in overcoming deficiencies of single therapy. Since excellent comprehensive reviews of stem cell-based therapy and NTFs-based therapy for neurodegenerative diseases have been published[1-3,5,7,10], in this review, the combination of stem cells with NTFs and the MSC-exosomes for the treatment of neurodegenerative diseases is discussed, with an emphasis on the combination therapy.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common type of dementia, affecting approximately 55 million people worldwide[18]. AD, including the familial type and sporadic type, manifests with cognitive impairment. AD pathologies include senile plaques caused by excessive deposition of beta-amyloid (Aβ) due to abnormal degradation of extracellular amyloid precursor protein, neurofibrillary tangles formed by intracellular hyper-phosphorylated Tau, loss of cholinergic neurons, neuroinflammation, oxidative stress, and changes in such NTFs as NGF and BDNF[19,20]. Currently, drug therapies such as acetylcholinesterase inhibitors (donepezil, galantamine) and NMDA receptor antagonists (memantine) can only delay symptoms, but not relieve disease pathology or progression[21,22]. Studies have demonstrated that neurons derived from stem cells can integrate with existing neural networks and repair damaged neurons in the host brain, yielding improvements in learning and memory deficits[23], and that NTFs can improve symptoms and provide neuroprotective effects in AD[24,25].

NTFs such as NGF and BDNF play important roles in neuron survival and differentiation, synapse plasticity, learning, and memory[26,27]. NGF is secreted by the postsynaptic cortex and hippocampal neurons in precursor form (proNGF), which converts to the mature form (mNGF) upon interaction with the extracellular protease plasmin. Upon the NGF molecule binding to the receptor tropomyosin receptor kinase (Trk) A/p75, the complex is internalized and retroactively transported to cholinergic cell bodies in the basal forebrain, triggering cholinergic function and promoting the release of acetylcholine[28-30]. Both proNGF and mNGF can induce neurotrophic effects through TrkA, but proNGF can induce apoptotic signals by interacting with p75[31,32]. Interestingly, changes in NGF metabolism, accumulation of proNGF level, and reduction of mNGF level have been observed in the pathological process of AD. Higher proNGF levels not only induce pro-apoptotic signaling but also affect the receptors binding to mNGF, leading to retrograde atrophy of cholinergic neurons in the basal forebrain[32-34]. Since cholinergic cell bodies retain their sensitivity to NGF, NGF delivery is a potential method to restore cholinergic signaling in the cortex and hippocampus. BDNF, on the other hand, is a neurotrophic protein that is highly expressed in the brain and plays important roles in neuronal survival and differentiation, synaptic formation, and hippocampal long-term potentiation. These BDNF effects in the hippocampus are mediated by the Trk B receptor[35,36]. ProBDNF is a precursor form of BDNF that interacts with the p75 receptor to induce apoptosis. It has been demonstrated that in the AD brain, proBDNF and p75 receptors are increased, while BDNF and TrkB receptor are decreased, a situation conductive to apoptosis signaling[37-40]. Moreover, studies have shown that higher serum BDNF levels are associated with a slower rate of cognitive decline in AD patients[41].

NGF and BDNF have low stability and short half-life, and as such cannot effectively pass through the blood-brain barrier. Additionally, repeated direct delivery of NTFs may have serious peripheral side effects[42]. Stem cells can secrete neurotrophins to a certain degree to improve the survival of neurons, despite their lower cell survival, limited lifespan, and majority dying before they affect the injured area[30,43]. Recently, it has been reported that using stem cells as carriers to deliver NTFs to the AD brain can increase the survival rate of neurons, improve learning and memory, reduce Aβ deposition, promote neurogenesis, and inhibit neuron apoptosis and glial cell activation[25,44-50] (Table 1).

Transplantation of NSCs combined with NGF into AD rats led to significant improvement in learning and memory and supplemented basal forebrain cholinergic neurons[25]. Hippocampus transplantation of bone marrow stromal cells (BMSCs)-NGF also significantly improved learning and memory of AD rats, as compared with the BMSC-implanted group, suggesting that BMSCs were effective carriers for NGF delivery[44]. Lateral cerebral ventricle transplantation of human BDNF-modified NSCs elicited a better improvement in learning and memory than that achieved in the NSCs-implanted AD rats[45]. NSC transplantation into transected rat basal forebrain followed by BDNF injection into the lateral ventricle also led to better improvements in the number of cholinergic neurons and the ability of learning and memory than implantation of NSCs alone[46]. Lateral ventricle transplantation of the *BDNF* gene-modified BMSCs into the AD rat model significantly attenuated the nerve cell damage in the CA1 region of the hippocampus, leading to significant improvement in learning and memory[47]. The protective effect of MSCs on AD pathology was enhanced by MSCs-BDNF, suggesting that the BDNF supply from MSCs-BDNF was enough to prevent AD pathology[48]. Treatment of AD with BDNF-overexpressing NSCs has also shown to improve the vitality of NSCs, to increase the therapeutic potential of implanted NSCs, and to alleviate AD cognitive deficits[49]. Our previous study showed that transplanting BDNF-modified human umbilical cord MSCs-derived cholinergic neurons not only improved memory and learning but also reduced the expression of amyloid-associated protein Aβ levels and promoted neurogenesis in AD rats[50].

MSC-exosomes showed similar effects to MSCs on the stimulation of neurogenesis and alleviation of learning and memory impairment evaluated by Morris water maze and novel object recognition tests in AD mice bilaterally dentate gyrus injected with $A\beta_{1-42}$, suggesting the possibility of developing MSC-exosomes as a cell-free candidate of MSCs for AD treatment[51]. Hypoxia-preconditioned MSC-exosomes restored synaptic dysfunction, decreased amyloid plaque deposition and the Aβ levels, and reduced inflammatory responses, leading to learning and memory improvement in the APP/PS1 AD mice[52]. Human umbilical cord MSC-exosomes injection alleviated neuroinflammation by modulating the microglia activation and cleared Aβ deposition in the brains of AD mice, leading to cognition repairment[53]. Neocortex injection of BM-MSC-EVs effectively reduced the Aβ burden and the number of dystrophic neurites in the hippocampus and cortex of 3 to 5-mo-old (early stages) APPswe/PS1dE9 AD mice, indicating a potentiality to intervent AD in early stages[54].

Table 1 Combination therapy of stem cells with neurotrophic factors in Alzheimer's disease

Cell types	Neurotrophic factors	Study design and outcome	Ref.
NSCs	NGF	Embryonic rat NSCs were separated and induced by NGF-PEG-PLGA-NPs *in vitro*, and were transplanted into AD rats(lateral ventricular injected with 192IgG-saporin). The Morris water maze was used to evaluate learning and memory, followed by immunohistochemical staining for basal forebrain cholinergic neurons, hippocampal synaptophysin, and AchE fibers. The rats in the combined treatment group showed significant improvement in spatial learning as compared to the untreated AD model animals. The treated rats also showed significantly higher number of basal forebrain cholinergic neurons and fibers with AchE positivity, and higher expression of hippocampal the rats in the NSCs group.	Chen *et al*[25], 2015
BMSCs	NGF	When compared with BMSCs transplantation alone, BMSCs-NGF transplantated into the hippocampus of AD rats (bilaterally injected with Aβ) significantly improved learning and memory. The findings suggested efficient NGF delivery by BMSCs.	Li *et al*[44], 2008
NSCs	BDNF	The AD rat model was established by cutting the unilateral fibria-fornix of male rats. Lateral cerebral ventricle transplantation of the NSCs and NSCs-hBDNF provided behavioral amelioration of AD rats assessed *via* the Morris water maze, and the effect of NSCs-hBDNF was better than that of NSCs.	Zhao *et al*[45], 2005
NSCs	BDNF	Transected rat basal forebrain BrdU-labeled NSCs transplantation followed by lateral ventricle BDNF injection led to labeled NSCs differentiation into neurons and astrocytes in the basal forebrain. The rats in the NSCs and BDNF combination group showed better improvement in the number of cholinergic neurons, and learning and memory as compared to the other groups.	Xuan *et al*[46], 2008
MSCs	BDNF	*BDNF* gene-modified BM-MSCs were transplanted into the lateral ventricle of an AD rat model. Nerve cell damage in the CA1 region of the hippocampus was significantly attenuated. BDNF tyrosine kinase B mRNA and protein levels were significantly increased, and learning and memory were significantly improved.	Zhang *et al*[47], 2012

MSCs	BDNF	A unique neuronal culture of familial-type AD neurons was made from the 5x familial-type AD mouse, an amyloid precursor protein/PS1 transgenic mouse model, to investigate progressive neurodegeneration associated with AD pathology and the efficacy of MSCs-BDNF. Analyses of the expression of BDNF, synaptic markers and survival/apoptotic signals indicated that pathological features of cultured neurons could accurately mimic AD pathology. The protective effect of MSCs was enhanced by MSCs-BDNF. The BDNF supplied from MSCs-BDNF was sufficient to prevent AD pathology.	Song *et al*[48], 2015
NSCs	BDNF	Hippocampus transplanted NSCs-BDNF integrated into the local brain circuits of the 16-mo-old Tg2576 mice, improved the engrafted cells' viability, neuronal fate, neurite complexity, the synaptic density, and the cognitive deficits of the AD mice.	Wu *et al*[49], 2016
hUC-MSCs	BDNF	Right hippocampus transplantation of BDNF-modified hUC-MSCs-derived cholinergic-like neurons significantly improved spatial learning and memory in the AD rats assessed by Morris water maze testing, increased the release of acetylcholine, enhanced the activation of astrocytes and microglia, reduced the expression of Aβ and BACE1, and inhibited neuronal apoptosis detected by Western blotting, immunohistochemistry, immunofluorescence assay, and TUNEL assay.	Hu *et al*[50], 2019

Aβ: Beta-amyloid; AchE: Acetylcholine esterase; AD: Alzheimer's disease; BDNF: Brain-derived neurotrophic factor; BM-MSCs: Bone marrow-mesenchymal stromal cells; BMSCs: Bone marrow stromal cells; BMSCs-NGF: Nerve growth factor gene-modified bone marrow stromal cells; BrdU: 5'-Bromo-2'-deoxyuridine; hUC-MSCs: Human umbilical cord-mesenchymal stem cells; MSCs: Mesenchymal stem cells; MSCs-BDNF: Brain-derived neurotrophic factor-modified mesenchymal stem cells; NGF: Nerve growth factor; NGF-PEG-PLGA-NPs: Nerve growth factor-poly(ethylene glycol)-poly (lactic-co-glycolic acid)-nanoparticles; NSCs: Neural stem cells; NSCs-hBDNF: Human brain-derived neurotrophic factor-modified neural stem cells; TUNEL: TdT-mediated dUTP nick end labeling.

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common neurodegenerative disorder. The motor symptoms of PD mainly include rest tremor, rigidity, bradykinesia and postural instability, while common nonmotor symptoms include neuropsychiatric and sleep disorders as well as sensory and autonomic dysfunction[55]. The pathological feature of PD is progressive degeneration and loss of dopamine (DA) neurons in the midbrain substantia nigra. Symptoms arise when 50% of the DA neurons are lost[56]. Unfortunately, there is no cure or disease-modifying therapy available for PD at present. Commonly used symptom-relief medications include levodopa, carbidopa, DA agonists, anticholingeric agents, amantadine, and DA metabolism inhibitors. However, the currently available drugs often provide only partial symptom control and elicit frequent side effects, such as motor complications (known as dyskinesia and wearing-off[57]) and gastrointestinal and neuropsychiatric dysfunctions[55]. Considering that these therapies for PD do not treat the underlying pathology, alternative therapies are still intensively pursued, including those based on stem cells and NTFs[49,55].

The goal of stem cell-based therapy to treat PD is to replace degenerated and lost DA neurons in the substantia nigra with healthy ones or to prevent further neuron loss[7]. Moreover, investigations into the use of NTFs as therapeutic options for PD were prompted by their role in neuronal survival, differentiation and plasticity, their correlation with the disease (namely NTFs' deficiency), and the findings of replacement or enhancement of NTF signals providing neuronal protection in PD

models[58,59]. The first identified potential NTF to treat PD was GDNF, which is able to increase DA uptake and the survival of embryonic midbrain DA neurons[60]. GDNF has since received the most attention for clinical trials[55]. Cell-based GDNF delivery is currently recognized as an appropriate alternative for treatment of PD, following clinical trials of GDNF alone yielding mixed results[61]. MSCs are the most promising cellular vehicle to deliver NTFs for PD treatment, and MSCs engineered to overexpress GDNF or BDNF have received much attention[62-68] (Table 2).

In the PD rat model established by the injection of 6-hydroxydopamine (6-OHDA) , dopaminergic neuron sprouting increased as a result of striatum transplantation (at 4 d prior to injury) of MSCs transfected with a retrovirus to express GDNF[62]; in addition, unilateral striatum transplantation of GDNF-overexpressing human MSCs decreased amphetamine-induced rotations and improved DA fibers' rejuvenation[63]. In the lactacystin-induced neurotoxicity(in the medial forebrain bundle) PD rat model, intrastriatal injection (at 1 wk prior to injury) of BMSCs transduced with lentivirus to overexpress GDNF was protective against the neurotoxicity and led to significantly increased striatal DA levels and behavior recovery, as assessed by apomorphine-induced rotations[64]. In a MPTP-treated non-human primate PD model, striatum and substantia nigra transplantation of BM-MSCs genetically modified to overexpress GDNF resulted in increased striatum DA levels and improved contralateral limb function[65]. In a lipopolysaccharide-induced PD model, unilateral striatal transplantation of MSCs-GDNF provided local neuroprotection of dopaminergic terminals in the striatum of PD rats[66]. Transplantation of human (h)MSCs-BDNF into the unilateral 6-OHDA-lesioned substantia nigra also resulted in remarkable nigral tyrosine hydroxylase-positive cell hypertrophy, striatal tyrosine hydroxylase-staining increase, and amphetamine-induced motor symptom stabilization[67]. In another study of the 6-OHDA-lesioned PD rat model, prior to transplantation, MSCs were first induced to NTF-secreting cells by *in vitro* exposure to nystatin, L-glutamine, human epidermal growth factor, human basic fibroblast growth factor (hbFGF) and N2 for 72 h, then dibutyryl cyclic AMP, isobutylmethylxanthine, human platelet-derived growth factor, human neuregulin 1-β1/HRG1-β1 EGF domain, and hbFGF for 3d, resulting in aquintupled increase in BDNF expression and doubled increase in GDNF expression. The striatum transplantation of these induced MSCs improved the amphetamine-induced rotations behavior, and ameliorated DA deficits more efficaciously than uninduced MSCs[68]. A study investigating the combination of human umbilical vein mesenchymal stem cells (HUVMSCs)-derived dopaminergic-like cells with NGF in a PD rat model found that as compared to cell grafting only, combination therapy significantly promoted the survival of the grafted cells and increased the dopaminergic content, leading to significant motor function improvement[69].

A study investigating the therapeutic effects of MSC-secretome on the physiological recovery in a 6-OHDA rat PD model underwent substantia nigra and striatum injection of MSC-secretome and rotarod and staircase tests, and observed increased dopaminergic neurons and neuronal terminals in the injected areas and recovery in the motor performance of PD rats, indicating that MSC-secretome is a novel therapeutic strategy for PD[70]. In another 6-OHDA rat PD model, the injection of hBMSC- secretome induced higher levels of neuronal differentiation, led to the rescue of DA neurons and the recovery of behavioral performance in the staircase test[71].

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a fatal inherited neurodegenerative disorder; its hallmark motor, cognitive and psychiatric dysfunctions manifest upon the progressive deterioration of striatal GABAergic medium-sized spiny neurons caused by mutations in the huntingtin (*HTT*) gene, leading to increased polyglutamine repeats in the HTT protein[72,73]. Multiple possible neurodegenerative mechanisms of HD are currently under investigation, and this knowledge is anticipated to serve as a basis for the development of new HD therapies. The abilities of stem cells to rescue or replace the damaged and dying neurons, and to prevent further cell damage and death, make stem cell-based therapies promising for treatment of this neurodegenerative disease[74].

In HD, BDNF has been demonstrated to mediate striatal neuronal function and survival by providing neurotrophins and neuroprotection[75]. Studies have also revealed a reduction in BDNF levels in HD patients, which may contribute to the clinical manifestations[76]. In the striatum, the reduced levels of BDNF are partially due to function loss of the wild-type HTT protein, which assists in vesicle transport of BDNF, while the mutation of which has adverse effects on BDNF transcription,

Table 2 Combination therapy of stem cells with neurotrophic factors in Parkinson's disease

Cell types	Neurotrophic factors	Study design and outcome	Ref.
MSCs	GDNF	MSCs-GDNF transplantation induced a pronounced local trophic effect in the denervated striatum of the 6-OHDA PD rat model.	Moloney *et al*[62], 2010
MSCs	GDNF	Striatum transplantation of GDNF-releasing Notch-induced BM-MSCs(SB623 cells) significantly decreased amphetamine-induced rotation and promoted DA fiber activation of the 6-OHDA PD rat model.	Glavaski-Joksimovic *et al*[63], 2010
MSCs	GDNF	The intrastriatal transplantation of BMSCs-GDNF significantly rescued the DA neurons from lactacystin-induced neurotoxicity, with regard to behavioral recovery and striatal dopamine level increase of the lactacystin-lesioned PD rat model, established by intrastriatum transplantation of BMSCs-GDNF followed by lactacystin induction of a lesion at the median forebrain bundles 1 wk later.	Wu *et al*[64], 2010
MSCs	GDNF	MSCs-GDNF were transplanted into the unilateral striatum and SN of cynomolgus monkeys (PD monkey model) to investigate the protective function of MSCs-GDNF against MPTP-induced injury. Monkeys in the MSCs-GDNF group showed spared contralateral limbs' motor function and had higher dopamine level and enhanced dopamine uptake in the striatum of the grafted hemisphere.	Ren *et al*[65], 2013
MSCs	GDNF	The lipopolysaccharide-lesioned PD rat model was used to assess the ability of MSCs-GDNF to protect against lipopolysaccharide-induced neuroinflammation, neurodegeneration, and behavioral impairment. Both experimental groups received a unilateral intrastriatal transplantation of either MSCs-GDNF or MSCs-green fluorescent protein. Protection and/or sprouting of the dopaminergic neuron terminals was induced by the secreted GDNF in the striatum of PD rats.	Hoban *et al*[66], 2015
MSCs	BDNF	The signals and/or molecules that regulate BDNF expression/delivery were investigated in hMSCs cultures and the effect of epigenetically generated BDNF-secreting hMSCs were evaluated for their impact on intact and lesioned SN. Results showed that the amphetamine-induced motor symptoms were stabilized.	Somoza *et al*[67], 2010
MSCs	BDNF; GDNF	The intrastriatum transplantation of NTF-SCs posterior to the 6-OHDA lesion led to an obvious amelioration of amphetamine-induced rotations, and the damaged striatal dopaminergic nerve terminal network was regenerated.	Sadan *et al*[68], 2009

HUVMSCs	NGF	As compared to HUVMSCs-derived dopaminergic-like cells alone, combination with NGF significantly promoted the cell survival, increased the dopaminergic content, and improved motor function of PD rats.	Li *et al*[69], 2010

6-OHDA: 6-Hydroxydopamine; BDNF: Brain-derived neurotrophic factor; DA: Dopamine; GDNF: Glial cell line-derived neurotrophic factor; hMSCs: Human mesenchymal stem cells; HUVMSCs: Human umbilical vein mesenchymal stem cells; MSCs: Mesenchymal stem cells; NGF: Nerve growth factor; NTF: Neurotrophic factor; NTF-SCs: Neurotrophic factor-secreting stem cells; PD: Parkinson's disease; SN: Substantia nigra.

proper transport, and secretion[77]. BDNF administration was shown to be neuroprotective *in vitro*, to rat neurons containing mutant HTT, and *in vivo*, to the striatum of R6/1 mice[75,78]. Therefore, BDNF administration is considered another hopeful candidate for HD treatment. To this end, an interesting and widely characterized candidate therapy in which MSCs were engineered to secrete BDNF was developed and found to promote neuron survival and regeneration in HD[79-81] (Table 3).

Retrovirus-*BDNF*/*NGF* gene-modified MSCs were shown to produce a 6.8-fold and 4.6-fold increase in the expression of BDNF in stem cells and in cell culture media, respectively. All 4-mo-old YAC 128 mice bilateral striatum transplanted with unmodified MSCs or NGF/BDNF (alone or combination)-overexpressing MSCs, showed reduced clasping; in addition, mice transplanted with the BDNF-overexpressing MSCs showed the longest rotarod latencies and the least amount of striatum neuronal loss, restored striatum NeuN-positive cell counts to the level detected in wild-type (non-HD) mice. These findings demonstrated that BDNF-modified MSCs facilitated behavioral and histological recovery of YAC 128 HD mice[79]. Intrastriatal administration with human MSCs-BDNF to YAC128 and R6/2 transgenic HD mice demonstrated that the MSCs-BDNF treatment significantly reduced anxiety, attenuated striatal atrophy in the YAC128 mice, and increased the mean lifespan and neurogenesis-like activity of the R6/2 mice. These improvements were attributed to the enhancement of endogenous neurogenesis stimulation and maturation promoted by BDNF and various complementary therapeutic factors secreted by the MSCs[80]. Transplantation of embryonic stem cell-derived BDNF-overexpressing neural progenitors to three different HD mouse models - the quinolinic acid-lesioned model and the two genetic models R6/2 and N171-82Q - led to motor function improvement in the quinolinic acid-lesioned model, which may be due to enhanced neuronal and striatal differentiation, while only subtle effects were shown in the two genetic models. The difference in the behavior improvement can be attributed to the different cell survival rates in different models; this is in agreement with the finding that neural progenitor cells (NPCs) transplanted into the two transgenic mice lines usually show lower cell survival rate[81].

In an *in vitro* HD model of R6/2 mice-derived neuronal cells, exosomes derived from adipose stem cells (ASC-exo) significantly decreased the mHtt aggregates, reduced abnormal apoptotic protein level, mitochondrial dysfunction and cell apoptosis, suggesting a therapeutic potentiality of ASC-exo for HD[82].

AMYOTROPHIC LATERAL SCLEROSIS

Amyotrophic lateral sclerosis (ALS) is one of the neurodegenerative disorders involving progressive degeneration of both upper and lower motor neurons, leading to palsy and death ultimately in 3-5 years from onset[83]. Multiple underlying mechanisms are involved in ALS pathology, including glutamate excitotoxicity, oxidative and endoplasmic reticulum stress, mitochondrial dysfunction, microglial and astrocyte function abnormality, and neurotrophic support impairment[84]. There are currently only two available disease-modifying medicines - riluzole and edaravone - that have shown benefit, albeit slight and to a limited set of patients[85]. Given the complex ALS pathogenesis and limited drug efficacy, there is a remarkable urgency to find new therapies for ALS. Stem cell-based therapy holds great promise for treating ALS by providing both cell replacement and NTF delivery to target the multiple pathologies[86,87]. Stem cells available for ALS treatment include NSCs, MSCs, embryonic stem cells, induced pluripotent stem cells, and olfactory ensheathing stem cells[88].

NTFs might benefit ALS patients by protecting motor neurons and preventing disease progression[89]. Besides the replacement of degenerated motor neurons by stem cells, neurotrophic support also plays an important role in the motor neurons'

Table 3 Combination therapy of stem cells with neurotrophic factors in Huntington's disease

Cell types	Neurotrophic factors	Study design and outcome	Ref.
MSCs	BDNF; NGF	BM-MSCs were genetically engineered to overexpress BDNF and/or NGF, and were then injected into the striata of 4-mo-old YAC128 transgenic and wild-type mice to determine the effects on motor function. Transplantation of MSCs-BDNF may slowdown neurodegenerative processes and provide behavioral sparing in the YAC128 mouse model of HD.	Dey *et al*[79], 2010
MSCs	BDNF	MSCs-BDNF were intrastriatially transplanted into YAC128 and R6/2 transgenic (immune-suppressed HD model) mice. MSCs-BDNF transplantation reduced anxiety, decreased striatal atrophy in the YAC128 mice and prolonged the mean lifespan and increased neurogenesis of the R6/2 mice.	Pollock *et al*[80], 2016
ESCs-derived NPCs	BDNF	ESCs-derived BDNF-overexpressing NPCs were transplanted into a quinolinic acid-lesioned model and two transgenic mouse lines (R6/2 and N171-82Q). NPCs-BDNF had a significant effect on motor function recovery in quinolinic acid-lesioned mice, while the genetic mouse model had only slight improvement. Adult neurogenesis was preserved in a BDNF-dependent manner.	Zimmermann *et al*[81], 2016

BDNF: Brain-derived neurotrophic factor; BM-MSCs: Bone marrow-mesenchymal stem cells; ESCs: Embryonic stem cells; HD: Huntington's disease; MSCs: Mesenchymal stem cells; NGF: Nerve growth factor; NPCs: Neural progenitors.

survival and function[90]. Thus, it is reasonable to combine stem cells and NTFs for the treatment of ALS, especially by transplanting stem cells engineered to overexpress NTFs[91]. Indeed, it has been shown that transplantation of stem cells combined with specific growth factors can markedly preserve neuromuscular junctions, attenuate motor neuron death, delay onset, improve motor function, and prolong survival of the SOD1^{G93A} rat ALS model[92-100] (Table 4).

It has been reported that lumbar spinal cord transplantation of human NPCs genetically modified to secrete GDNF only limited motor neuron degeneration in the SOD1^{G93A} ALS rats[92,93], while cortex transplantation also prolonged the lifespan[94]. On the other hand, bilateral intramuscular transplantation of human(h)MSCs-GDNF led to survival of the hMSCs and release of GDNF into the muscle of the SOD1^{G93A}ALS rats, which increased the number of neuromuscular connections and prevented the loss of motor neurons in the spinal cord, leading to delayed disease progression and increased lifespan (by 28 d)[95]. Similarly, intrathecal transplantation of human NSCs overexpressing VEGF into the SOD1^{G93A} ALS mice delayed disease onset and prolonged lifespan[96]. In addition, combination therapy of intranasal NGF administration with lateral ventricle NSCs transplantation also delayed disease onset, improved motor function and extended survival of the SOD1^{G93A}ALS mice[97].

In order to determine whether the effect of hMSCs-GDNF on slowing the progression of the disease could be enhanced by multiple NTFs, hMSCs-GDNF, hMSCs-VEGF, hMSCs-IGF-1, or hMSCs-BDNF were transplanted bilaterally into muscles of the SOD1^{G93A}ALS rats. Compared to individual NTF delivery, intramuscular delivery of hMSCs-GDNF combined with hMSCs-VEGF demonstrated synergic and greater effects on increasing survival rate, preventing motor neuron degeneration, and protecting neuromuscular junction[98]. In addition, transplantation of muscle progenitor cells-MIX (a mixture of muscle progenitor cells expressing BDNF, GDNF, VEGF, or IGF-1) into the hind legs of the SOD1^{G93A}ALS mice, decreased neuromuscular junction degeneration and increased axonal survival, leading to delayed disease onset (by 30 d) and prolonged survival (by 13 d). These results demonstrated that continuous delivery of the mixture of NTFs by engineered muscle progenitor cells might be a beneficial therapy for ALS[99]. In 2016, there were a phase 1/2 and a phase 2a clinical trials transplanting NTF-secreting BM-MSCs to small

Table 4 Combination therapy of stem cells with neurotrophic factors in amyotrophic lateral sclerosis

Cell types	Neurotrophic factors	Study design and outcome	Ref.
hNPCs	GDNF	hNPCs-GDNF were transplanted into the lumbar spinal cord of SOD1^{G93A} ALS rats. Genetically-modified hNPCs were able to survive, integrate, and release GDNF in the spinal cord of SOD1^{G93A} rats.	Klein *et al*[92], 2005
hNPCs	GDNF	hNPCs-GDNF were unilaterally transplanted into the spinal cord of SOD1^{G93A} ALS rats. There was robust cellular migration into degenerated areas, efficient delivery of GDNF and remarkable preservation of motor neurons at early and end stages of the disease.	Suzuki *et al*[93], 2007
hNPCs	GDNF	hNPCs-GDNF were unilaterally transplanted into the motor cortex of SOD1^{G93A} ALS rats. The hNPCs-GDNF matured into astrocytes, and released GDNF, which protected motor neurons, delayed disease pathology, and extended survival of theSOD1^{G93A} rats.	Thomsen *et al*[94], 2018
hMSCs	GDNF	hMSCs-GDNF were transplanted bilaterally into three muscle groups of a fALS rat model. Transplanted cells survived within the muscle, released GDNF, and increased the number of neuromuscular connections. Direct muscle delivery of hMSCs-GDNF ameliorated motor neuron loss within the spinal cord, delayed disease progression, and increased overall lifespan by 28 d.	Suzuki *et al*[95], 2008
hNSCs	VEGF	hNSCs overexpressing VEGF were IT transplanted into SOD1^{G93A} mice. Intrathecal hNSCs-VEGF transplantation significantly delayed disease onset and prolonged survival of the SOD1^{G93A} mice.	Hwang *et al*[96], 2009
NSCs	NGF	Intranasal NGF administration combined with lateral ventricle NSCs transplantation to the SOD1^{G93A}ALS mice delayed onset, improved motor function and prolonged lifespan.	Zhong *et al*[97], 2017
hMSCs	GDNF; VEGF; IGF-I; BDNF	To determine whether multiple NTFs played a synergistic role of slowing disease progression, SOD1^{G93A} rats were bilaterally muscularly transplanted with hMSCs-GDNF, hMSCs-VEGF, hMSCs-IGF-I, or hMSCs-BDNF. hMSCs-GDNF and hMSCs-VEGF prolonged survival and slowed the loss of motor function, and the combined delivery of GDNF and VEGF showed a strong synergistic effect.	Krakora *et al*[98], 2013
MPCs	BDNF; GDNF; VEGF; IGF-1	Hind legs transplantation of MPCs-MIX, a mixture of MPCs expressing BDNF, GDNF, VEGF, or IGF-1,decreased neuromuscular junction degeneration, increased axonal survival, delayed onset and prolonged lifespan of the SOD1 ^{G93A} mice.	Dadon-Nachum *et al*[99], 2015

MSCs	GDNF; BDNF; VEGF; HGF	To determine the safety and possible clinical efficacy of autologous MSCs-NTF cells transplantation in ALS patients. All patients were followed for 3 mo before the transplantation and for 6 mo after the transplantation. In the phase 1/2 part of the trial, 6 patients with early-stage ALS were injected IM and 6 patients with more advanced disease were transplanted IT. In the second stage, a phase 2a dose-escalating study, 14 patients with early-stage ALS received a combined IM and IT transplantation of autologous MSCs-NTF. Treatment of ALS patients with autologous MSCs-NTF cells by IT, IM, or combined (IT+IM) administration was safe and well tolerated. The rate of progression of forced vital capacity and ALS Functional Rating Scale-Revised score in the IT (or IT+IM)-treated patients were reduced.	Petrou *et al*[100], 2016 (clinical trials)

ALS: Amyotrophic lateral sclerosis; BDNF: Brain-derived neurotrophic factor; fALS: Familial amyotrophic lateral sclerosis: GDNF: Glial cell line-derived neurotrophic factor; HGF: Hepatocyte growth factor; hMSCs: Human mesenchymal stem cells; hNPCs: Human neural progenitor cells; hNPCs-GDNF: Lentivirus-modified hNPCs secreting GDNF; hNSCs: Human neural stem cells; IGF-1: Insulin-like growth factor-1; IM: Intramuscularly; IT: Intrathecally; MPCs: Muscle progenitor cells; MSCs-NTF: Neurotrophic factor secreting mesenchymal stem cells; NGF: Nerve growth factor; NSCs: Neural stem cells; NTF: Neurotrophic factor; VEGF: Vascular endothelial growth factor.

groups of ALS patients. Different administration methods were evaluated for patients in different stages of the disease, with early patients transplanted intramuscularly and progressive ones transplanted intrathecally. Results showed reduced progression rate of forced vital capacity and ALS Functional Rating Scale-Revised score in the intrathecal (or intrathecal plus intramuscular)-treated patients. Clinical trials have since shown that both routes of administration are safe, but the possible clinical benefits need to be confirmed by a larger cohort study[100].

In *in vitro* ALS models, adipose-derived stromal cells derived exosomes (ASC-exosomes) showed neuroprotection through oxidative damage protection, mitochondria function restoration and anti-apoptosis effects, indicating that ASC-exosomes is a promising approach to treat ALS[101-103].

CONCLUSION

Neurodegenerative diseases are a large group of neurological disorders characterized by progressive neuronal degeneration and loss, leading to motor and cognition impairment and ultimately death of affected patients. There is currently a lack of effective treatments for all neurodegenerative diseases because of their obscure pathogeneses. However, studies have revealed the considerable therapeutic promise of stem cells and NTFs, and especially when used in combination. The combination therapy of stem cells with NTFs – generated by engineering stem cells to overexpress NTFs, that is, using stem cells as a delivery platform for NTFs - can not only replenish the target neurons but also secrete neurotrophins to improve the microenvironment for nerve repair and regeneration. However, different neurodegenerative diseases exhibit specific neuron type loss, with cholinergic neurons in AD, dopaminergic neurons in PD, projection neurons in HD, and motor neurons in ALS. Thus, future research should give priority to the use of stem cell-derived disease-specific cell types in combination with cell-specific NTFs. Given the great promise of stem cells in combination with NTFs in clinical application, this novel treatment avenue is expected to provide benefit to patients suffering from neurodegenerative diseases in the future.

REFERENCES

1 **Volkman R**, Offen D. Concise Review: Mesenchymal Stem Cells in Neurodegenerative Diseases. *Stem Cells* 2017; **35**: 1867-1880 [PMID: 28589621 DOI: 10.1002/stem.2651]
2 **Xiao N**, Le QT. Neurotrophic Factors and Their Potential Applications in Tissue Regeneration. *Arch*

Immunol Ther Exp (Warsz) 2016; **64**: 89-99 [PMID: 26611762 DOI: 10.1007/s00005-015-0376-4]
3 **Pramanik S**, Sulistio YA, Heese K. Neurotrophin Signaling and Stem Cells-Implications for Neurodegenerative Diseases and Stem Cell Therapy. *Mol Neurobiol* 2017; **54**: 7401-7459 [PMID: 27815842 DOI: 10.1007/s12035-016-0214-7]
4 **Lunn JS**, Sakowski SA, Hur J, Feldman EL. Stem cell technology for neurodegenerative diseases. *Ann Neurol* 2011; **70**: 353-361 [PMID: 21905078 DOI: 10.1002/ana.22487]
5 **Staff NP**, Jones DT, Singer W. Mesenchymal Stromal Cell Therapies for Neurodegenerative Diseases. *Mayo Clin Proc* 2019; **94**: 892-905 [PMID: 31054608 DOI: 10.1016/j.mayocp.2019.01.001]
6 **Gorabi AM**, Kiaie N, Barreto GE, Read MI, Tafti HA, Sahebkar A. The Therapeutic Potential of Mesenchymal Stem Cell-Derived Exosomes in Treatment of Neurodegenerative Diseases. *Mol Neurobiol* 2019; **56**: 8157-8167 [PMID: 31197655 DOI: 10.1007/s12035-019-01663-0]
7 **Joyce N**, Annett G, Wirthlin L, Olson S, Bauer G, Nolta JA. Mesenchymal stem cells for the treatment of neurodegenerative disease. *Regen Med* 2010; **5**: 933-946 [PMID: 21082892 DOI: 10.2217/rme.10.72]
8 **Lo Furno D**, Mannino G, Giuffrida R. Functional role of mesenchymal stem cells in the treatment of chronic neurodegenerative diseases. *J Cell Physiol* 2018; **233**: 3982-3999 [PMID: 28926091 DOI: 10.1002/jcp.26192]
9 **Poduslo JF**, Curran GL. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Brain Res Mol Brain Res* 1996; **36**: 280-286 [PMID: 8965648 DOI: 10.1016/0169-328x(95)00250-v]
10 **Kotzbauer PT**, Holtzman DM. Expectations and challenges in the therapeutic use of neurotrophic factors. *Ann Neurol* 2006; **59**: 444-447 [PMID: 16489617 DOI: 10.1002/ana.20794]
11 **Scheper V**, Schwieger J, Hamm A, Lenarz T, Hoffmann A. BDNF-overexpressing human mesenchymal stem cells mediate increased neuronal protection in vitro. *J Neurosci Res* 2019; **97**: 1414-1429 [PMID: 31257632 DOI: 10.1002/jnr.24488]
12 **Wyse RD**, Dunbar GL, Rossignol J. Use of genetically modified mesenchymal stem cells to treat neurodegenerative diseases. *Int J Mol Sci* 2014; **15**: 1719-1745 [PMID: 24463293 DOI: 10.3390/ijms15021719]
13 **Raposo G**, Stoorvogel W. Extracellular vesicles: exosomes, microvesicles, and friends. *J Cell Biol* 2013; **200**: 373-383 [PMID: 23420871 DOI: 10.1083/jcb.201211138]
14 **Kalani A**, Tyagi A, Tyagi N. Exosomes: mediators of neurodegeneration, neuroprotection and therapeutics. *Mol Neurobiol* 2014; **49**: 590-600 [PMID: 23999871 DOI: 10.1007/s12035-013-8544-1]
15 **Yeo RW**, Lai RC, Zhang B, Tan SS, Yin Y, Teh BJ, Lim SK. Mesenchymal stem cell: an efficient mass producer of exosomes for drug delivery. *Adv Drug Deliv Rev* 2013; **65**: 336-341 [PMID: 22780955 DOI: 10.1016/j.addr.2012.07.001]
16 **Vilaça-Faria H**, Salgado AJ, Teixeira FG. Mesenchymal Stem Cells-derived Exosomes: A New Possible Therapeutic Strategy for Parkinson's Disease? *Cells* 2019; 8 [PMID: 30717429 DOI: 10.3390/cells8020118]
17 **Joo HS**, Suh JH, Lee HJ, Bang ES, Lee JM. Current Knowledge and Future Perspectives on Mesenchymal Stem Cell-Derived Exosomes as a New Therapeutic Agent. *Int J Mol Sci* 2020; **21** [PMID: 31979113 DOI: 10.3390/ijms21030727]
18 **Alzheimer's Association**. 2016 Alzheimer's disease facts and figures. *Alzheimers Dement* 2016; **12**: 459-509 [PMID: 27570871 DOI: 10.1016/j.jalz.2016.03.001]
19 **Strac DS**, Muck-Seler D, Pivac N. Neurotransmitter measures in the cerebrospinal fluid of patients with Alzheimer's disease: a review. *Psychiatr Danub* 2015; **27**: 14-24 [PMID: 25751428]
20 **Scheltens P**, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. *Lancet* 2016; **388**: 505-517 [PMID: 26921134 DOI: 10.1016/S0140-6736(15)01124-1]
21 **Deardorff WJ**, Feen E, Grossberg GT. The Use of Cholinesterase Inhibitors Across All Stages of Alzheimer's Disease. *Drugs Aging* 2015; **32**: 537-547 [PMID: 26033268 DOI: 10.1007/s40266-015-0273-x]
22 **Kishi T**, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's Disease: An Updated Systematic Review and Meta-analysis. *J Alzheimers Dis* 2017; **60**: 401-425 [PMID: 28922160 DOI: 10.3233/JAD-170424]
23 **Alipour M**, Nabavi SM, Arab L, Vosough M, Pakdaman H, Ehsani E, Shahpasand K. Stem cell therapy in Alzheimer's disease: possible benefits and limiting drawbacks. *Mol Biol Rep* 2019; **46**: 1425-1446 [PMID: 30565076 DOI: 10.1007/s11033-018-4499-7]
24 **Blurton-Jones M**, Kitazawa M, Martinez-Coria H, Castello NA, Müller FJ, Loring JF, Yamasaki TR, Poon WW, Green KN, LaFerla FM. Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *Proc Natl Acad Sci USA* 2009; **106**: 13594-13599 [PMID: 19633196 DOI: 10.1073/pnas.0901402106]
25 **Chen Y**, Pan C, Xuan A, Xu L, Bao G, Liu F, Fang J, Long D. Treatment Efficacy of NGF Nanoparticles Combining Neural Stem Cell Transplantation on Alzheimer's Disease Model Rats. *Med Sci Monit* 2015; **21**: 3608-3615 [PMID: 26590375 DOI: 10.12659/msm.894567]
26 **Vilar M**, Mira H. Regulation of Neurogenesis by Neurotrophins during Adulthood: Expected and Unexpected Roles. *Front Neurosci* 2016; **10**: 26 [PMID: 26903794 DOI: 10.3389/fnins.2016.00026]
27 **Leal G**, Bramham CR, Duarte CB. BDNF and Hippocampal Synaptic Plasticity. *Vitam Horm* 2017; **104**: 153-195 [PMID: 28215294 DOI: 10.1016/bs.vh.2016.10.004]
28 **Campenot RB**, MacInnis BL. Retrograde transport of neurotrophins: fact and function. *J Neurobiol* 2004; **58**: 217-229 [PMID: 14704954 DOI: 10.1002/neu.10322]
29 **Biane J**, Conner JM, Tuszynski MH. Nerve growth factor is primarily produced by GABAergic neurons of the adult rat cortex. *Front Cell Neurosci* 2014; **8**: 220 [PMID: 25147503 DOI: 10.3389/fncel.2014.00220]
30 **Mitra S**, Behbahani H, Eriksdotter M. Innovative Therapy for Alzheimer's Disease-With Focus on Biodelivery of NGF. *Front Neurosci* 2019; **13**: 38 [PMID: 30804738 DOI: 10.3389/fnins.2019.00038]
31 **Bradshaw RA**, Pundavela J, Biarc J, Chalkley RJ, Burlingame AL, Hondermarck H. NGF and ProNGF: Regulation of neuronal and neoplastic responses through receptor signaling. *Adv Biol Regul* 2015; **58**: 16-27 [PMID: 25491371 DOI: 10.1016/j.jbior.2014.11.003]
32 **Ioannou MS**, Fahnestock M. ProNGF, but Not NGF, Switches from Neurotrophic to Apoptotic Activity in Response to Reductions in TrkA Receptor Levels. *Int J Mol Sci* 2017; **18** [PMID: 28282920 DOI: 10.3390/ijms18030599]
33 **Iulita MF**, Cuello AC. Nerve growth factor metabolic dysfunction in Alzheimer's disease and Down syndrome. *Trends Pharmacol Sci* 2014; **35**: 338-348 [PMID: 24962069 DOI: 10.1016/j.tips.2014.04.010]

34 **Allard S**, Jacobs ML, Do Carmo S, Cuello AC. Compromise of cortical proNGF maturation causes selective retrograde atrophy in cholinergic nucleus basalis neurons. *Neurobiol Aging* 2018; **67**: 10-20 [PMID: 29609077 DOI: 10.1016/j.neurobiolaging.2018.03.002]

35 **Lu B**, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. *Nat Rev Neurosci* 2013; **14**: 401-416 [PMID: 23674053 DOI: 10.1038/nrn3505]

36 **Ng TKS**, Ho CSH, Tam WWS, Kua EH, Ho RC. Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis. *Int J Mol Sci* 2019; **20** [PMID: 30634650 DOI: 10.3390/ijms20020257]

37 **Fleitas C**, Piñol-Ripoll G, Marfull P, Rocandio D, Ferrer I, Rampon C, Egea J, Espinet C. proBDNF is modified by advanced glycation end products in Alzheimer's disease and causes neuronal apoptosis by inducing p75 neurotrophin receptor processing. *Mol Brain* 2018; **11**: 68 [PMID: 30428894 DOI: 10.1186/s13041-018-0411-6]

38 **Chakravarthy B**, Ménard M, Ito S, Gaudet C, Dal Prà I, Armato U, Whitfield J. Hippocampal membrane-associated p75NTR levels are increased in Alzheimer's disease. *J Alzheimers Dis* 2012; **30**: 675-684 [PMID: 22451321 DOI: 10.3233/JAD-2012-120115]

39 **Saadipour K**, Mañucat-Tan NB, Lim Y, Keating DJ, Smith KS, Zhong JH, Liao H, Bobrovskaya L, Wang YJ, Chao MV, Zhou XF. p75 neurotrophin receptor interacts with and promotes BACE1 localization in endosomes aggravating amyloidogenesis. *J Neurochem* 2018; **144**: 302-317 [PMID: 28869759 DOI: 10.1111/jnc.14206]

40 **Forlenza OV**, Diniz BS, Teixeira AL, Radanovic M, Talib LL, Rocha NP, Gattaz WF. Lower Cerebrospinal Fluid Concentration of Brain-Derived Neurotrophic Factor Predicts Progression from Mild Cognitive Impairment to Alzheimer's Disease. *Neuromolecular Med* 2015; **17**: 326-332 [PMID: 26138246 DOI: 10.1007/s12017-015-8361-y]

41 **Laske C**, Stellos K, Hoffmann N, Stransky E, Straten G, Eschweiler GW, Leyhe T. Higher BDNF serum levels predict slower cognitive decline in Alzheimer's disease patients. *Int J Neuropsychopharmacol* 2011; **14**: 399-404 [PMID: 20860877 DOI: 10.1017/S1461145710001008]

42 **Thoenen H**, Sendtner M. Neurotrophins: from enthusiastic expectations through sobering experiences to rational therapeutic approaches. *Nat Neurosci* 2002; **5** Suppl: 1046-1050 [PMID: 12403983 DOI: 10.1038/nn938]

43 **Liu Y**, Weick JP, Liu H, Krencik R, Zhang X, Ma L, Zhou GM, Ayala M, Zhang SC. Medial ganglionic eminence-like cells derived from human embryonic stem cells correct learning and memory deficits. *Nat Biotechnol* 2013; **31**: 440-447 [PMID: 23604284 DOI: 10.1038/nbt.2565]

44 **Li LY**, Li JT, Wu QY, Li J, Feng ZT, Liu S, Wang TH. Transplantation of NGF-gene-modified bone marrow stromal cells into a rat model of Alzheimer' disease. *J Mol Neurosci* 2008; **34**: 157-163 [PMID: 18074108 DOI: 10.1007/s12031-007-9022-x]

45 **Zhao Z**, Hu H, Feng G. [Learning and memory amelioration of transplantation of the neural stem cells modified with human brain-derived neurotrophic factor gene on Alzheimer disease model rat]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi* 2005; **19**: 331-334 [PMID: 15960430 DOI: 10.1016/j.chaos.2004.11.066]

46 **Xuan AG**, Long DH, Gu HG, Yang DD, Hong LP, Leng SL. BDNF improves the effects of neural stem cells on the rat model of Alzheimer's disease with unilateral lesion of fimbria-fornix. *Neurosci Lett* 2008; **440**: 331-335 [PMID: 18579298 DOI: 10.1016/j.neulet.2008.05.107]

47 **Zhang P**, Zhao G, Kang X, Su L. Effects of lateral ventricular transplantation of bone marrow-derived mesenchymal stem cells modified with brain-derived neurotrophic factor gene on cognition in a rat model of Alzheimer's disease. *Neural Regen Res* 2012; **7**: 245-250 [PMID: 25806063 DOI: 10.3969/j.issn.1673-5374.2012.04.001]

48 **Song MS**, Learman CR, Ahn KC, Baker GB, Kippe J, Field EM, Dunbar GL. In vitro validation of effects of BDNF-expressing mesenchymal stem cells on neurodegeneration in primary cultured neurons of APP/PS1 mice. *Neuroscience* 2015; **307**: 37-50 [PMID: 26297896 DOI: 10.1016/j.neuroscience.2015.08.011]

49 **Wu CC**, Lien CC, Hou WH, Chiang PM, Tsai KJ. Gain of BDNF Function in Engrafted Neural Stem Cells Promotes the Therapeutic Potential for Alzheimer's Disease. *Sci Rep* 2016; **6**: 27358 [PMID: 27264956 DOI: 10.1038/srep27358]

50 **Hu W**, Feng Z, Xu J, Jiang Z, Feng M. Brain-derived neurotrophic factor modified human umbilical cord mesenchymal stem cells-derived cholinergic-like neurons improve spatial learning and memory ability in Alzheimer's disease rats. *Brain Res* 2019; **1710**: 61-73 [PMID: 30586546 DOI: 10.1016/j.brainres.2018.12.034]

51 **Reza-Zaldivar EE**, Hernández-Sapiéns MA, Gutiérrez-Mercado YK, Sandoval-Ávila S, Gomez-Pinedo U, Márquez-Aguirre AL, Vázquez-Méndez E, Padilla-Camberos E, Canales-Aguirre AA. Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. *Neural Regen Res* 2019; **14**: 1626-1634 [PMID: 31089063 DOI: 10.4103/1673-5374.255978]

52 **Cui GH**, Wu J, Mou FF, Xie WH, Wang FB, Wang QL, Fang J, Xu YW, Dong YR, Liu JR, Guo HD. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. *FASEB J* 2018; **32**: 654-668 [PMID: 28970251 DOI: 10.1096/fj.201700600R]

53 **Ding M**, Shen Y, Wang P, Xie Z, Xu S, Zhu Z, Wang Y, Lyu Y, Wang D, Xu L, Bi J, Yang H. Exosomes Isolated From Human Umbilical Cord Mesenchymal Stem Cells Alleviate Neuroinflammation and Reduce Amyloid-Beta Deposition by Modulating Microglial Activation in Alzheimer's Disease. *Neurochem Res* 2018; **43**: 2165-2177 [PMID: 30259257 DOI: 10.1007/s11064-018-2641-5]

54 **Elia CA**, Tamborini M, Rasile M, Desiato G, Marchetti S, Swuec P, Mazzitelli S, Clemente F, Anselmo A, Matteoli M, Malosio ML, Coco S. Intracerebral Injection of Extracellular Vesicles from Mesenchymal Stem Cells Exerts Reduced Aβ Plaque Burden in Early Stages of a Preclinical Model of Alzheimer's Disease. *Cells* 2019; **8** [PMID: 31510042 DOI: 10.3390/cells8091059]

55 **Staudt MD**, Di Sebastiano AR, Xu H, Jog M, Schmid S, Foster P, Hebb MO. Advances in Neurotrophic Factor and Cell-Based Therapies for Parkinson's Disease: A Mini-Review. *Gerontology* 2016; **62**: 371-380 [PMID: 26330171 DOI: 10.1159/000438701]

56 **Fearnley JM**, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 1991; **114**: 2283-2301 [PMID: 1933245 DOI: 10.1093/brain/114.5.2283]

57 **Bargiotas P**, Konitsiotis S. Levodopa-induced dyskinesias in Parkinson's disease: emerging treatments.

Neuropsychiatr Dis Treat 2013; **9**: 1605-1617 [PMID: 24174877 DOI: 10.2147/NDT.S36693]
58 **Rodrigues TM**, Jerónimo-Santos A, Outeiro TF, Sebastião AM, Diógenes MJ. Challenges and promises in the development of neurotrophic factor-based therapies for Parkinson's disease. *Drugs Aging* 2014; **31**: 239-261 [PMID: 24610720 DOI: 10.1007/s40266-014-0160-x]
59 **Aron L**, Klein R. Repairing the parkinsonian brain with neurotrophic factors. *Trends Neurosci* 2011; **34**: 88-100 [PMID: 21144600 DOI: 10.1016/j.tins.2010.11.001]
60 **Pascual A**, Hidalgo-Figueroa M, Gómez-Díaz R, López-Barneo J. GDNF and protection of adult central catecholaminergic neurons. *J Mol Endocrinol* 2011; **46**: R83-R92 [PMID: 21357726 DOI: 10.1530/JME-10-0125]
61 **Kitada M**, Dezawa M. Parkinson's disease and mesenchymal stem cells: potential for cell-based therapy. *Parkinsons Dis* 2012; **2012**: 873706 [PMID: 22530164 DOI: 10.1155/2012/873706]
62 **Moloney TC**, Rooney GE, Barry FP, Howard L, Dowd E. Potential of rat bone marrow-derived mesenchymal stem cells as vehicles for delivery of neurotrophins to the Parkinsonian rat brain. *Brain Res* 2010; **1359**: 33-43 [PMID: 20732313 DOI: 10.1016/j.brainres.2010.08.040]
63 **Glavaski-Joksimovic A**, Virag T, Mangatu TA, McGrogan M, Wang XS, Bohn MC. Glial cell line-derived neurotrophic factor-secreting genetically modified human bone marrow-derived mesenchymal stem cells promote recovery in a rat model of Parkinson's disease. *J Neurosci Res* 2010; **88**: 2669-2681 [PMID: 20544825 DOI: 10.1002/jnr.22435]
64 **Wu J**, Yu W, Chen Y, Su Y, Ding Z, Ren H, Jiang Y, Wang J. Intrastriatal transplantation of GDNF-engineered BMSCs and its neuroprotection in lactacystin-induced Parkinsonian rat model. *Neurochem Res* 2010; **35**: 495-502 [PMID: 19894114 DOI: 10.1007/s11064-009-0086-6]
65 **Ren Z**, Wang J, Wang S, Zou C, Li X, Guan Y, Chen Z, Zhang YA. Autologous transplantation of GDNF-expressing mesenchymal stem cells protects against MPTP-induced damage in cynomolgus monkeys. *Sci Rep* 2013; **3**: 2786 [PMID: 24071770 DOI: 10.1038/srep02786]
66 **Hoban DB**, Howard L, Dowd E. GDNF-secreting mesenchymal stem cells provide localized neuroprotection in an inflammation-driven rat model of Parkinson's disease. *Neuroscience* 2015; **303**: 402-411 [PMID: 26166730 DOI: 10.1016/j.neuroscience.2015.07.014]
67 **Somoza R**, Juri C, Baes M, Wyneken U, Rubio FJ. Intranigral transplantation of epigenetically induced BDNF-secreting human mesenchymal stem cells: implications for cell-based therapies in Parkinson's disease. *Biol Blood Marrow Transplant* 2010; **16**: 1530-1540 [PMID: 20542127 DOI: 10.1016/j.bbmt.2010.06.006]
68 **Sadan O**, Bahat-Stromza M, Barhum Y, Levy YS, Pisnevsky A, Peretz H, Ilan AB, Bulvik S, Shemesh N, Krepel D, Cohen Y, Melamed E, Offen D. Protective effects of neurotrophic factor-secreting cells in a 6-OHDA rat model of Parkinson disease. *Stem Cells Dev* 2009; **18**: 1179-1190 [PMID: 19243240 DOI: 10.1089/scd.2008.0411]
69 **Li M**, Zhang SZ, Guo YW, Cai YQ, Yan ZJ, Zou Z, Jiang XD, Ke YQ, He XY, Jin ZL, Lu GH, Su DQ. Human umbilical vein-derived dopaminergic-like cell transplantation with nerve growth factor ameliorates motor dysfunction in a rat model of Parkinson's disease. *Neurochem Res* 2010; **35**: 1522-1529 [PMID: 20658188 DOI: 10.1007/s11064-010-0211-6]
70 **Teixeira FG**, Carvalho MM, Panchalingam KM, Rodrigues AJ, Mendes-Pinheiro B, Anjo S, Manadas B, Behie LA, Sousa N, Salgado AJ. Impact of the Secretome of Human Mesenchymal Stem Cells on Brain Structure and Animal Behavior in a Rat Model of Parkinson's Disease. *Stem Cells Transl Med* 2017; **6**: 634-646 [PMID: 28191785 DOI: 10.5966/sctm.2016-0071]
71 **Mendes-Pinheiro B**, Anjo SI, Manadas B, Da Silva JD, Marote A, Behie LA, Teixeira FG, Salgado AJ. Bone Marrow Mesenchymal Stem Cells' Secretome Exerts Neuroprotective Effects in a Parkinson's Disease Rat Model. *Front Bioeng Biotechnol* 2019; **7**: 294 [PMID: 31737616 DOI: 10.3389/fbioe.2019.00294]
72 **Landles C**, Bates GP. Huntingtin and the molecular pathogenesis of Huntington's disease.Fourth in molecular medicine review series. *EMBO Rep* 2004; **5**: 958-963 [PMID: 15459747 DOI: 10.1038/sj.embor.7400250]
73 **Estrada Sánchez AM**, Mejía-Toiber J, Massieu L. Excitotoxic neuronal death and the pathogenesis of Huntington's disease. *Arch Med Res* 2008; **39**: 265-276 [PMID: 18279698 DOI: 10.1016/j.arcmed.2007.11.011]
74 **Maucksch C**, Vazey EM, Gordon RJ, Connor B. Stem cell-based therapy for Huntington's disease. *J Cell Biochem* 2013; **114**: 754-763 [PMID: 23097329 DOI: 10.1002/jcb.24432]
75 **Canals JM**, Pineda JR, Torres-Peraza JF, Bosch M, Martín-Ibañez R, Muñoz MT, Mengod G, Ernfors P, Alberch J. Brain-derived neurotrophic factor regulates the onset and severity of motor dysfunction associated with enkephalinergic neuronal degeneration in Huntington's disease. *J Neurosci* 2004; **24**: 7727-7739 [PMID: 15342740 DOI: 10.1523/JNEUROSCI.1197-04.2004]
76 **Zuccato C**, Ciammola A, Rigamonti D, Leavitt BR, Goffredo D, Conti L, MacDonald ME, Friedlander RM, Silani V, Hayden MR, Timmusk T, Sipione S, Cattaneo E. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* 2001; **293**: 493-498 [PMID: 11408619 DOI: 10.1126/science.1059581]
77 **Zuccato C**, Cattaneo E. Role of brain-derived neurotrophic factor in Huntington's disease. *Prog Neurobiol* 2007; **81**: 294-330 [PMID: 17379385 DOI: 10.1016/j.pneurobio.2007.01.003]
78 **Zala D**, Benchoua A, Brouillet E, Perrin V, Gaillard MC, Zurn AD, Aebischer P, Déglon N. Progressive and selective striatal degeneration in primary neuronal cultures using lentiviral vector coding for a mutant huntingtin fragment. *Neurobiol Dis* 2005; **20**: 785-798 [PMID: 16006135 DOI: 10.1016/j.nbd.2005.05.017]
79 **Dey ND**, Bombard MC, Roland BP, Davidson S, Lu M, Rossignol J, Sandstrom MI, Skeel RL, Lescaudron L, Dunbar GL. Genetically engineered mesenchymal stem cells reduce behavioral deficits in the YAC 128 mouse model of Huntington's disease. *Behav Brain Res* 2010; **214**: 193-200 [PMID: 20493905 DOI: 10.1016/j.bbr.2010.05.023]
80 **Pollock K**, Dahlenburg H, Nelson H, Fink KD, Cary W, Hendrix K, Annett G, Torrest A, Deng P, Gutierrez J, Nacey C, Pepper K, Kalomoiris S, D Anderson J, McGee J, Gruenloh W, Fury B, Bauer G, Duffy A, Tempkin T, Wheelock V, Nolta JA. Human Mesenchymal Stem Cells Genetically Engineered to Overexpress Brain-derived Neurotrophic Factor Improve Outcomes in Huntington's Disease Mouse Models. *Mol Ther* 2016; **24**: 965-977 [PMID: 26765769 DOI: 10.1038/mt.2016.12]
81 **Zimmermann T**, Remmers F, Lutz B, Leschik J. ESC-Derived BDNF-Overexpressing Neural Progenitors Differentially Promote Recovery in Huntington's Disease Models by Enhanced Striatal Differentiation. *Stem Cell Reports* 2016; **7**: 693-706 [PMID: 27693427 DOI: 10.1016/j.stemcr.2016.08.018]

82 **Lee M**, Liu T, Im W, Kim M. Exosomes from adipose-derived stem cells ameliorate phenotype of Huntington's disease in vitro model. *Eur J Neurosci* 2016; **44**: 2114-2119 [PMID: 27177616 DOI: 10.1111/ejn.13275]

83 **Rowland LP**, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001; **344**: 1688-1700 [PMID: 11386269 DOI: 10.1056/NEJM200105313442207]

84 **Bruijn LI**, Miller TM, Cleveland DW. Unraveling the mechanisms involved in motor neuron degeneration in ALS. *Annu Rev Neurosci* 2004; **27**: 723-749 [PMID: 15217349 DOI: 10.1146/annurev.neuro.27.070203.144244]

85 **Fujimori K**, Ishikawa M, Otomo A, Atsuta N, Nakamura R, Akiyama T, Hadano S, Aoki M, Saya H, Sobue G, Okano H. Modeling sporadic ALS in iPSC-derived motor neurons identifies a potential therapeutic agent. *Nat Med* 2018; **24**: 1579-1589 [PMID: 30127392 DOI: 10.1038/s41591-018-0140-5]

86 **Faravelli I**, Riboldi G, Nizzardo M, Simone C, Zanetta C, Bresolin N, Comi GP, Corti S. Stem cell transplantation for amyotrophic lateral sclerosis: therapeutic potential and perspectives on clinical translation. *Cell Mol Life Sci* 2014; **71**: 3257-3268 [PMID: 24699704 DOI: 10.1007/s00018-014-1613-4]

87 **Lunn JS**, Sakowski SA, Feldman EL. Concise review: Stem cell therapies for amyotrophic lateral sclerosis: recent advances and prospects for the future. *Stem Cells* 2014; **32**: 1099-1109 [PMID: 24448926 DOI: 10.1002/stem.1628]

88 **Czarzasta J**, Habich A, Siwek T, Czapliński A, Maksymowicz W, Wojtkiewicz J. Stem cells for ALS: An overview of possible therapeutic approaches. *Int J Dev Neurosci* 2017; **57**: 46-55 [PMID: 28088365 DOI: 10.1016/j.ijdevneu.2017.01.003]

89 **Morren JA**, Galvez-Jimenez N. Current and prospective disease-modifying therapies for amyotrophic lateral sclerosis. *Expert Opin Investig Drugs* 2012; **21**: 297-320 [PMID: 22303913 DOI: 10.1517/13543784.2012.657303]

90 **Henriques A**, Pitzer C, Schneider A. Neurotrophic growth factors for the treatment of amyotrophic lateral sclerosis: where do we stand? *Front Neurosci* 2010; **4**: 32 [PMID: 20592948 DOI: 10.3389/fnins.2010.00032]

91 **Lunn JS**, Hefferan MP, Marsala M, Feldman EL. Stem cells: comprehensive treatments for amyotrophic lateral sclerosis in conjunction with growth factor delivery. *Growth Factors* 2009; **27**: 133-140 [PMID: 19294549 DOI: 10.1080/08977190902814855]

92 **Klein SM**, Behrstock S, McHugh J, Hoffmann K, Wallace K, Suzuki M, Aebischer P, Svendsen CN. GDNF delivery using human neural progenitor cells in a rat model of ALS. *Hum Gene Ther* 2005; **16**: 509-521 [PMID: 15871682 DOI: 10.1089/hum.2005.16.509]

93 **Suzuki M**, McHugh J, Tork C, Shelley B, Klein SM, Aebischer P, Svendsen CN. GDNF secreting human neural progenitor cells protect dying motor neurons, but not their projection to muscle, in a rat model of familial ALS. *PLoS One* 2007; **2**: e689 [PMID: 17668067 DOI: 10.1371/journal.pone.0000689]

94 **Thomsen GM**, Avalos P, Ma AA, Alkaslasi M, Cho N, Wyss L, Vit JP, Godoy M, Suezaki P, Shelest O, Bankiewicz KS, Svendsen CN. Transplantation of Neural Progenitor Cells Expressing Glial Cell Line-Derived Neurotrophic Factor into the Motor Cortex as a Strategy to Treat Amyotrophic Lateral Sclerosis. *Stem Cells* 2018; **36**: 1122-1131 [PMID: 29656478 DOI: 10.1002/stem.2825]

95 **Suzuki M**, McHugh J, Tork C, Shelley B, Hayes A, Bellantuono I, Aebischer P, Svendsen CN. Direct muscle delivery of GDNF with human mesenchymal stem cells improves motor neuron survival and function in a rat model of familial ALS. *Mol Ther* 2008; **16**: 2002-2010 [PMID: 18797452 DOI: 10.1038/mt.2008.197]

96 **Hwang DH**, Lee HJ, Park IH, Seok JI, Kim BG, Joo IS, Kim SU. Intrathecal transplantation of human neural stem cells overexpressing VEGF provide behavioral improvement, disease onset delay and survival extension in transgenic ALS mice. *Gene Ther* 2009; **16**: 1234-1244 [PMID: 19626053 DOI: 10.1038/gt.2009.80]

97 **Zhong SJ**, Gong YH, Lin YC. Combined intranasal nerve growth factor and ventricle neural stem cell grafts prolong survival and improve disease outcome in amyotrophic lateral sclerosis transgenic mice. *Neurosci Lett* 2017; **656**: 1-8 [PMID: 28694091 DOI: 10.1016/j.neulet.2017.07.005]

98 **Krakora D**, Mulcrone P, Meyer M, Lewis C, Bernau K, Gowing G, Zimprich C, Aebischer P, Svendsen CN, Suzuki M. Synergistic effects of GDNF and VEGF on lifespan and disease progression in a familial ALS rat model. *Mol Ther* 2013; **21**: 1602-1610 [PMID: 23712039 DOI: 10.1038/mt.2013.108]

99 **Dadon-Nachum M**, Ben-Yaacov K, Ben-Zur T, Barhum Y, Yaffe D, Perlson E, Offen D. Transplanted modified muscle progenitor cells expressing a mixture of neurotrophic factors delay disease onset and enhance survival in the SOD1 mouse model of ALS. *J Mol Neurosci* 2015; **55**: 788-797 [PMID: 25330859 DOI: 10.1007/s12031-014-0426-0]

100 **Petrou P**, Gothelf Y, Argov Z, Gotkine M, Levy YS, Kassis I, Vaknin-Dembinsky A, Ben-Hur T, Offen D, Abramsky O, Melamed E, Karussis D. Safety and Clinical Effects of Mesenchymal Stem Cells Secreting Neurotrophic Factor Transplantation in Patients With Amyotrophic Lateral Sclerosis: Results of Phase 1/2 and 2a Clinical Trials. *JAMA Neurol* 2016; **73**: 337-344 [PMID: 26751635 DOI: 10.1001/jamaneurol.2015.4321]

101 **Bonafede R**, Scambi I, Peroni D, Potrich V, Boschi F, Benati D, Bonetti B, Mariotti R. Exosome derived from murine adipose-derived stromal cells: Neuroprotective effect on in vitro model of amyotrophic lateral sclerosis. *Exp Cell Res* 2016; **340**: 150-158 [PMID: 26708289 DOI: 10.1016/j.yexcr.2015.12.009]

102 **Calabria E**, Scambi I, Bonafede R, Schiaffino L, Peroni D, Potrich V, Capelli C, Schena F, Mariotti R. ASCs-Exosomes Recover Coupling Efficiency and Mitochondrial Membrane Potential in an *in vitro* Model of ALS. *Front Neurosci* 2019; **13**: 1070 [PMID: 31680811 DOI: 10.3389/fnins.2019.01070]

103 **Bonafede R**, Brandi J, Manfredi M, Scambi I, Schiaffino L, Merigo F, Turano E, Bonetti B, Marengo E, Cecconi D, Mariotti R. The Anti-Apoptotic Effect of ASC-Exosomes in an In Vitro ALS Model and Their Proteomic Analysis. *Cells* 2019; **8** [PMID: 31540100 DOI: 10.3390/cells8091087]

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