

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

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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

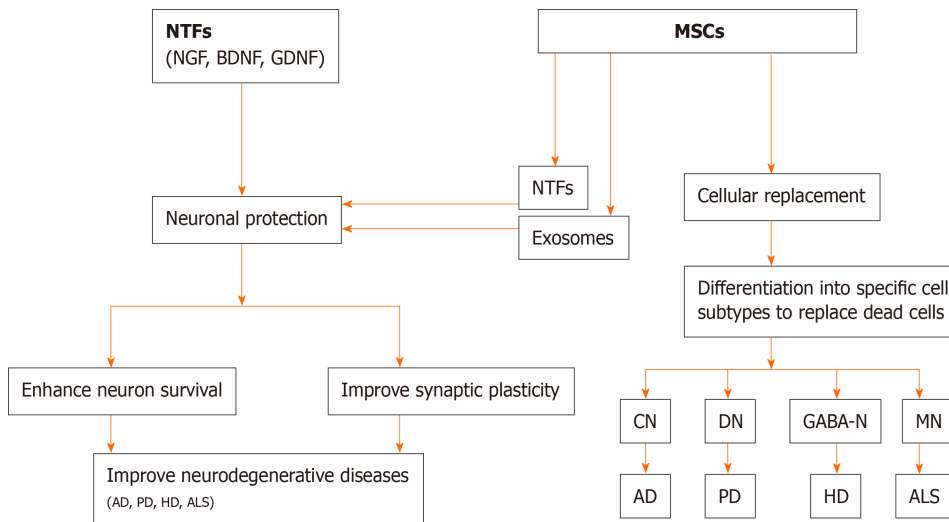


Figure 1 Possible effects of mesenchymal stem cells and neurotrophic factors for Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis. AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; BDNF: Brain-derived neurotrophic factor; CN: Cholinergic neurons; 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 inability 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 ($A\beta$) 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 conducive 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 A β 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 A β 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 β 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 A β 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 A β deposition in the brains of AD mice, leading to cognition repairment^[53]. Neocortex injection of BM-MSC-EVs effectively reduced the A β 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 <i>in vitro</i> , 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 <i>et al</i> ^[25] , 2015
BMSCs	NGF	When compared with BMSCs transplantation alone, BMSCs-NGF transplanted into the hippocampus of AD rats (bilaterally injected with A β) significantly improved learning and memory. The findings suggested efficient NGF delivery by BMSCs.	Li <i>et al</i> ^[44] , 2008
NSCs	BDNF	The AD rat model was established by cutting the unilateral fimbria-fornix of male rats. Lateral cerebral ventricle transplantation of the NSCs and NSCs-hBDNF provided behavioral amelioration of AD rats assessed <i>via</i> the Morris water maze, and the effect of NSCs-hBDNF was better than that of NSCs.	Zhao <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 A β and BACE1, and inhibited neuronal apoptosis detected by Western blotting, immunohistochemistry, immunofluorescence assay, and TUNEL assay.	Hu <i>et al</i> ^[50] , 2019

A β : 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, anticholinergic 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- β 1/HRG1- β 1 EGF domain, and hbFGF for 3d, resulting in a quintupled 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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al.</i> ^[69] , 2010
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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 <i>et al</i> ^[79] , 2010
MSCs	BDNF	MSCs-BDNF were intrastriatally 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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 the SOD1 ^{G93A} rats.	Thomsen <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[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 <i>et al</i> ^[100] , 2016 (clinical trials)
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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 pathogenesis. 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.

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