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Mesenchymal Stromal Cell Therapies for Neurodegenerative Diseases

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Abstract

Mesenchymal stromal cells are multipotent cells that are being used to treat a variety of medical conditions. Over the past decade, there has been considerable excitement about using MSCs to treat neurodegenerative diseases, which are diseases that are typically fatal and without other robust therapies. In this review, we discuss the proposed MSC mechanisms of action in neurodegenerative diseases, which include growth factor secretion, exosome secretion, and attenuation of neuroinflammation. We then provide a summary of preclinical and early clinical work on MSC therapies in amyotrophic lateral sclerosis, multiple system atrophy, Parkinson's disease, and Alzheimer's disease. Continued rigorous and controlled studies of MSC therapies will be critical in order to establish efficacy and protect patients from possible untoward side effects.

Neurodegenerative diseases are a broad class of disorders characterized by progressive neuronal death that leads to debilitating neurological impairments. Examples of ultimately fatal neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and multiple system atrophy (MSA). While there have been significant advances in the symptomatic management of these diseases that improve quality of life and at times survival, the available medications likely only slow the progression of neuronal death by a few months. The idea of using cell therapy to treat neurodegenerative diseases has been around for decades, most notably in PD where a variety of cell transplant investigations have been performed with varying success.[1] Mesenchymal stromal cells (also sometimes referred to as mesenchymal stem cells; MSCs; see recent commentary by Sipp et al., for discussion about the nomenclature controversy)[2] are multipotent cells that have become increasingly studied as a therapy for a variety of neurological diseases. As of October 2018, there were 939 clinical studies listed at www.clinicaltrials.gov that report using MSCs. 218 of these clinical studies are for diseases of the nervous system, making them the most represented system in the body (Table 1). As MSCs have entered clinical trials for devastating neurodegenerative diseases, the excitement and interest in MSCs has become at times fevered. This, in part, has led to many for-profit entities that provide MSC therapies for a range of diseases, some of which make dubious

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claims and have unclear product safety. Conversely, rigorous basic science and clinical research are being performed widely in this rapidly growing and exciting field. In this review, we aim to discuss MSC therapeutic modes of action and how these cells are being utilized in neurodegenerative disease preclinical models and early phase clinical trials.

MSCs secrete growth factors and modulate immune system

While MSCs are considered to be a type of stem cell, they have limited differentiation capacity. Unlike embryonic (or induced) pluripotent stem cells, which may differentiate into all cell types, MSCs are primarily limited to differentiating into cells of mesenchymal origin (fibroblast, osteocyte, adipocyte, chondrocyte). It is still controversial whether MSCs can be readily differentiated into cells of endodermal or ectodermal (including neuronal) fates. Therefore, it is not expected that MSCs would mediate any beneficial effect by incorporating into neuronal networks to replace dying neurons, which may be anticipated in other neural stem cell approaches.

MSCs reside within several tissues *in vivo*, including adipose, bone marrow, Wharton's jelly, and dental pulp, and may arise from pericytes[3]. They are further defined by the International Society for Cellular Therapy as expressing CD90, CD73, CD105 and CD44 while not expressing CD45 and CD31. [4, 5] Within the body, it is thought that normal MSC function is to migrate to areas of injury and participate in the reparative process.[6] Both allogeneic and autologous MSC therapies are in development. Unlike most other allogeneic cell therapies in clinical development, allogeneic MSC therapies may be used without concomitant immunosuppression due to their paucity of MHC Class II proteins and decreased propensity to trigger an immune response.[7]

The precise mechanism by which MSCs may exert beneficial effects in neurological disease is still being elucidated, but it appears that multiple different mechanisms may contribute (Figure). First, MSCs have been shown to secrete neurotrophic growth factors, including glial cell-derived neurotrophic factor (GDNF), vascular endothelial growth factor, and brain-derived neurotrophic factor (BDNF),[8, 9] which can be further enhanced under specific culture conditions.[10] Neurotrophic growth factors have been shown to improve neuronal survival in a number of preclinical models of neuron injury, including ALS, PD, and MSA transgenic animals [11–17] and nerve injury models. [12, 18, 19] Second, MSCs strongly modulate the immune system and can aid wound healing, and this mechanism has been exploited in disorders such as graft versus host disease[20] and Crohn's disease.[21] From a neurodegenerative perspective, it has become increasingly recognized that neuroinflammation plays a significant pathomechanistic role. Neuroinflammation in this context is defined as the negative contribution of non-neuronal cells (immune cells, glial cells, etc.) to neurodegenerative disease. While all of the details are not worked out, it is clear that activated microglia, astrocytes, and T-cells are able to interact and increase neuronal death due to proinflammatory and reactive oxygen species production.[22,23] Interestingly, MSCs may be either anti-inflammatory or pro-inflammatory depending on the milieu within which they exist. When entering an inflammatory milieu (interferon-gamma, tumor necrosis factor-alpha), MSCs become anti-inflammatory wherein they secrete transforming growth factor-beta1, indoleamine-2,3-dioxygenase, and prostaglandin E2 and

can convert macrophage/microglia from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype.[24] Furthermore, MSCs can induce upregulation of forkhead box P3+ regulatory T cells, which are thought to play a key role in ALS.[25]

MSCs mediate their immunomodulatory effects via direct cell-cell interactions, but also have strong paracrine influences via secreted cytokines and growth factors. One of the key methods that MSCs secrete biological factors is via extracellular vesicles (EVs), which are divided into either microvesicles (> 200nm diameter that are exocytosed from plasma membrane) or exosomes (50-200 nm diameter that arise from endosomal trafficking).[26] EVs are packed with thousands of proteins,[27] mRNA, and/or microRNA,[28] many of which are enriched in EVs compared to MSCs, and have been demonstrated to enhance neuronal growth and health in model systems.[29–31] Given that much of MSC paracrine actions are mediated via EVs, these subcellular packages are being developed as a cell-free biological therapeutic in their own right, which would obviate the theoretical teratogenic concerns of cell therapy.

Finally, an intriguing new hypothesis to explain the positive effects of MSCs is they may improve neuronal health by donating their mitochondria.[32] This mechanism of mitochondrial transfer has been observed between astrocytes and neurons in stroke model,[33] as well as between MSCs and alveoli in a lung injury model.[34] Through this mechanism, MSCs conceivably could improve neuronal health by donating healthy mitochondria to neurons that harbor dysfunctional mitochondria.

MSC therapy for neurodegenerative diseases

MSCs are being investigated as a therapy for a host of neurological diseases, and clinical trials have been performed in cerebrovascular diseases[35–37] and inflammatory demyelinating disorders.[38, 39] In this review, we will focus on data gathered in the study of neurodegenerative diseases, which have overlapping neuroinflammatory pathomechanisms that MSC therapy may impact. Table 2 lists all clinical trials for the below conditions that are registered with ClinicalTrials.gov and are signified as “recruiting”, “enrolling by invitation”, “active not recruiting”, or “not yet recruiting”.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal paralytic neurodegenerative disorder due to death of motor neurons in the brain and spinal cord.[40] The median lifespan following symptom onset is 3 years. The only medications that alter the disease course are riluzole and edaravone. Riluzole decreases glutamate excitotoxicity, but only prolongs life for ~3 months and edaravone was recently approved, but is currently without demonstrated survival benefit data (although it is presumed). Several mechanisms have been implicated in the pathogenesis of ALS and insights from hereditary forms of ALS strongly implicate RNA processing and protein aggregation as key early steps in the disease initiation. Two primary mechanisms of MSC putative benefits, neurotrophic growth factor secretion and neuroinflammation modulation, have been targets for ALS therapy development for years.

There is considerable evidence from animal studies that neurotrophic factors (Insulin-like Growth Factor-1, BDNF, GDNF, etc.) may slow neurodegeneration.[11, 13, 14, 18, 41–45] Unfortunately, subsequent human studies have not confirmed a benefit for patients.[46–48] The reason for this lack of concurrence between the results of animal model studies and subsequent human trials may be because the animals do not faithfully model the human disease, because therapeutic agents are handled differently in animal systems compared with humans, or because clinical trials have been too short or inadequately sensitive to detect the degree of change detectable in animal models.[49] The role of the blood brain barrier may also be relevant, and notably some of the most compelling animal studies have used direct delivery of growth factors into the CNS.[14] This mode of delivery has not been thoroughly investigated in human trials.[50–52]

The role of neuroinflammation in ALS has been hypothesized since the 1970's, but recent data has increased the recognition of this mechanism.[53] Microglia and inflammatory leukocytes are thought to be key players in this process and there are alterations of these cells in autopsies of patients with ALS.[54, 55] While it is not clear whether neuroinflammation causes ALS, it is theorized that it greatly determines the rate of disease progression. For example, in transgenic Superoxide dismutase-1 (SOD-1) rodent models of ALS, it has been shown that mutant SOD-1 in motor neurons primarily determines disease onset, whereas mutant SOD-1 in astrocytes and the immune system primarily determines the rate of progression.[56–59] Human studies have also demonstrated abnormalities in the peripheral immune system in ALS patients.[60–68] More data supporting the role of the immune system in ALS has arisen from studies of leukocyte microRNA, where specific upregulation of distinct microRNA has been reported in people with ALS,[69–71] and treatment of these leukocytes in animal models ameliorates the disease.[69, 72]

Animal studies of MSCs in ALS have been promising. MSCs can be safely infused into the intrathecal space of animals and survive for up to 6 months after injection.[73–77] Animal models of ALS have revealed MSC therapeutic potential, with efficacy data in several preclinical studies in ALS,[78–89] including MSC conditioned-media[81] and exosomes.[79]

Early phase human clinical trials have been completed using MSC treatment in ALS and demonstrate a favorable safety profile. Our group recently studied the effect of intrathecal therapy with autologous adipose-derived MSCs in a Phase I, dose-escalation study. Overall, the safety was acceptable, with some temporary back/leg pain at the highest tested doses.[90] Other groups have found similar safety profiles using naïve bone marrow-derived MSCs[91–93] and bone marrow-derived MSCs cultured to enhance neurotrophic factor secretion.[94] While none of these studies were designed to study efficacy, there did not appear to be any worsening of ALS progression rates, and there were some signs that suggested benefit.[90–95] These studies have now progressed to ongoing Phase M/MI clinical trials.

Alzheimer's Disease

Dementia is a progressive neurodegenerative disorder of the brain that alters normal cognition to such a degree that an individual is no longer able to function independently in society. Alzheimer's disease (AD) is the most common cause of dementia. The typical

clinical dementia syndrome associated with AD is that of a slowly progressive decline in memory appearing early in the clinical phase of the disease.[96] As the disease progresses, other cognitive domains become involved. Atypical clinical presentations of AD occur with initial prominent symptoms in visual-spatial, motor, language, or executive functioning.[97] AD is a progressive degenerative disorder with associated clinical symptoms during life, but the definitive diagnosis can only be made on the post-mortem examination of the brain. The classic neuropathological features are neuritic plaques and neurofibrillary tangles.[98] Biomarkers, such as amyloid positron emission tomography, have been shown to predict AD pathology[99] allowing for the characterization of these processes *in vivo* during life. The pathologic changes that are characteristic of AD are known to occur decades before clinical symptoms are present leading to a long preclinical prodromal disease phase[100] before progressing to mild cognitive impairment[101] and then dementia.[102] Recent biomarker criteria for diagnosing the AD continuum during life for research purpose have recently been proposed.[103] These research criteria will be important for future clinical trials, especially in preclinical phases of AD where therapeutics are hoped to be most effective before cognitive symptoms and pathologic changes become irreversible. Once MSCs trials have progressed to large clinical trials in humans, the entire AD continuum (preclinical, mild cognitive impairment, and dementia) and the heterogeneity in clinical symptoms should be carefully considered during trial design.

It has long been known that the pathologic hallmarks of AD (i.e., plaques and neurofibrillary tangles) are composed of beta-amyloid and tau protein aggregates. However, the pathogenic mechanisms that drive the association between these protein aggregates and the clinical symptoms are not known. A wide-array of global, molecular, and cellular processes have been hypothesized to play a role in AD pathogenies including network failure[104], pathologic plasticity,[105] mitochondrial dysfunction,[106] innate immunity,[107] inflammation,[108] autophagy[109], and toxicity of protein aggregates and oligomers like amyloid.[110] The ability of MSCs to secrete neurotrophic factors may improve the cellular milieu and limit cell loss in the setting of this complex AD pathophysiology. In addition, MSCs' known immunomodulatory effects may limit the damage effects of activated glial cell related synaptic pruning and inflammation in general. MSCs also have the potential to deliver a healthy supply of mitochondria to the CNS thereby mitigating the impact of age and AD-related mitochondrial dysfunction.

In amyloid precursor protein/presenilin 1 mouse models of AD, bone marrow-derived MSCs have been shown to reduce microglia cell counts, but not to alter the number of amyloid plaques.[111] However, others have seen a decrease in amyloid deposits with bone marrow-derived MSCs[112] consistent with what has been reported using human umbilical cord derived MSCs to rescue memory deficits and reduce amyloid-beta deposition in an amyloid precursor protein/presenilin 1 transgenic mouse.[113] The effect of MSCs on mouse models of AD pathology and cognition may be mediated through modulatory effects on neuroinflammation.[114] This same group also postulated that inhibition of apoptosis[115] may also be playing a role. Others have reported enhanced neurogenesis via the Wnt signaling pathway in the hippocampus is playing an important role in the effect of MSC on mouse models of AD.[116] There has not been a detailed study of the effects of MSC on

mitochondrial function in mouse models of AD. Human trials in AD are under development.[117]

Multiple System Atrophy

MSA is a rare sporadic and fatal multi-system progressive disorder characterized by progressive autonomic failure (including orthostatic hypotension, neurogenic bladder, and erectile dysfunction), cerebellar ataxia, corticospinal dysfunction, and parkinsonism that is often poorly responsive to levodopa therapy (unlike PD)[118]. The disease is relentlessly progressive with a median survival from diagnosis to death of approximately 3 years.[119–121] MSA represents one of the motor synucleinopathies which also include PD and diffuse Lewy body disease. Neuropathologically, these conditions are linked by positivity of inclusions to α-synuclein with reduced solubility.[122] But in contrast to neuronal α-synuclein (Lewy bodies), MSA is characterized by glial cytoplasmic inclusions of abnormally aggregated α-synuclein, primarily found in the striatum, cerebellum, brainstem, cortex, and spinal cord, regions also associated with the most pronounced neuronal loss.[123–125] Many lines of evidence highlight the pathological importance of α-synuclein aggregation, and disease progression is thought to be directly linked to accumulation and aggregation of conformationally changed α-synuclein.[126–129] Although the precise mechanisms by which α-synuclein aggregation leads to neuronal loss are not completely understood, there are a number of downstream effects contributing to neuronal pathology. A central mechanism appears to be that of glial dysfunction with resulting deficiency of growth factors, especially BDNF and GDNF, which are critical for neuronal survival.[130] Another important mechanism appears to be neuroinflammation as microglial activation can be demonstrated in certain, stages of the pathophysiologic cascade.[131, 132] Lastly, although glial cytoplasmic inclusions are the primary neuropathological hallmark of MSA, neuronal cytoplasmic and nuclear inclusions of α-synuclein have also been reported.[125, 133] Furthermore, recent work with transgenic models suggests that neuronal/oligodendroglial propagation of α-synuclein may partake in the pathophysiology of MSA.[128]

The ability of MSCs to produce and secrete neurotrophic factors known to be deficient in MSA, and MSCs' known immunomodulatory effects therefore provide a compelling rationale for the pursuit of delivering MSCs with therapeutic intent. Such an approach is further supported by animal studies demonstrating that human MSCs have a protective effect against progressive dopaminergic and striatal neuronal loss.[15, 16] Recently, the neuroprotective and immunomodulatory effects of MSCs were confirmed in a transgenic mouse model of MSA.[17]

When applied to humans, the blood brain barrier comprises a potential hurdle in cell delivery to the central nervous system. Although it has been shown that this barrier is less tight in MSA, it remains a major hurdle for MSC access.[134] Since growth factors also do not generally cross the blood-brain barrier, the desired effects may not reach target neurons in the relevant areas of brain if delivered systemically.[135, 136] In order to reach those areas of interest, strategies have to be pursued to efficiently and safely overcome that barrier.

In a first human study utilizing MSC delivery to patients with MSA, a Korean group pursued an open-label study of 29 patients with MSA, of which 11 received bone marrow-derived

MSCs while 18 did not.[137] A total of 4×10^7 MSCs were administered as infusions into both internal carotid arteries and the dominant vertebral artery. Additionally, patients received 3 subsequent intravenous MSC injections. The investigators compared the clinical course between MSC-treated and control patients and reported significantly less progression based on clinical assessments using the unified MSA rating scale in MSC-treated patients compared to control patients at all visits throughout the 12-month study period. Serial positron emission tomography scans in the MSC-treated group showed increased fluorodeoxyglucose uptake from baseline in cerebellum and frontal white matter while fluorodeoxyglucose uptake in the follow-up scan of the control group decreased significantly in the cerebellum and brainstem. No serious adverse effects related to MSC therapy occurred, although transient ischemic changes, evident on MRI, without clinical correlate, were seen with the intra-arterial infusions.[137] The same group published the results of a double-blind placebo controlled single-center study on 33 subjects in 2012.[138] Although the effect was less dramatic than what was observed in the open-label study, this trial confirmed a significantly smaller increase in total and unified MSA rating scale scores (part II) compared with the placebo group. Concordantly, cerebral glucose metabolism and gray matter density showed less decrease in the cerebellum and the cerebral cortical areas in the MSC compared to the placebo group. Again seen were small ischemic lesions on magnetic resonance imaging as a result of intra-arterial infusions which were asymptomatic except for one patient who developed basal ganglia infarcts with transient dystonia.[138]

We have since pursued a phase I/II dose-escalation trial utilizing a different approach to overcoming the blood-brain barrier and allowing for more widespread CNS delivery: the intrathecal route. 24 patients with probable MSA based on clinical consensus criteria and autonomic testing were enrolled and received escalating doses of adipose-derived MSCs ranging from one injection of 1×10^7 to two injections (one month apart) of 1×10^8 cells each. The primary aim of this study was to determine the safety and tolerability of this approach, and secondary aims relate to exploring signals of potential efficacy using clinical, autonomic, and imaging markers. This study has recently been completed and the manuscript is currently under review. Findings were sufficiently intriguing to pursue an ongoing compassionate extension study.

Parkinson's disease

PD is the most common synucleinopathy and the second most common neurodegenerative disease after AD, with a prevalence of approximately 1% in people over 60 years of age in industrialized countries.[139] PD is clinically characterized by a combination of tremor, bradykinesia, and rigidity, but a number of non-motor symptoms and findings commonly associated with PD, including cognitive dysfunction, mood disorders, sleep disturbances, autonomic dysfunction, go beyond the classification of PD as a movement disorder.[140–144] The pathologic hallmark of PD are Lewy bodies - intracytoplasmic neuronal alpha-synuclein inclusions - and neuronal loss in selected areas within the brain, including substantia nigra, locus ceruleus, dorsal vagal nucleus, and cerebral cortex; however, Lewy pathology is also found in spinal cord, sympathetic ganglia, as well as the cardiac and myenteric plexus.[145–149] Cardiac sympathetic noradrenergic denervation is also a common finding.[150] The precise mechanisms leading to neuronal loss in PD are incompletely understood, but appear

to be multifactorial and include genetic factors, oxidative stress, glial dysfunction and lack of trophic factors, excitotoxicity, inflammation, and mitochondrial dysfunction.[151–154]

Considering the ability of MSCs to secrete neurotrophic factors, modulate inflammation, and possibly even act as mitochondria “donor”, it comes as no surprise that there is a lot of interest in the use of MSCs in the treatment of PD, and a multitude of animal studies has shown promise. Direct striatal administration of bone marrow-derived MSCs with or without prior use of neuronal differentiation medium resulted in improvement of motor function, protection of the nigrostriatal system, and improved striatal dopamine release in several studies using toxic lesion rodent models of PD [155–162] as well as a proteasome model of PD [16]. Similar effects were reported with adipose-derived and umbilical cord-derived MSCs with or without prior differentiation.[163–170] For example, in a study using autologous transplantation into the substantia nigra, McCoy and colleagues reported improvement of motor function, reduced microglial activation, and decreased loss of TH immunoreactivity, associated with local production of trophic factors.[165] Intrastriatal administration was furthermore shown to enhance neurogenesis in the subventricular zone and to induce neuroblast migration to the striatum.[167,171]

Similar findings were reported with venous administration of MSCs in some studies, but concerns have been expressed about the non-selectivity of this administration route, limited crossing of the blood-brain barrier, and lack of long-term survival. [16, 172–177] A study on intracarotid infusion of MSCs in the brain of rats bearing a 6-hydroxydopamine-induced lesion of the nigrostriatal tract showed that the infused cells did not efficiently cross the blood-brain barrier without using a permeabilizing agent.[178] MSCs were detected in various brain regions, but there was no convincing modification of the progression of motor impairment. A study using intranasal administration showed neuroprotective and anti-inflammatory effects with localization of MSCs documented in the olfactory bulb, cortex, hippocampus, striatum, cerebellum, brainstem, amygdala, hippocampus and spinal cord; MSCs were still found in these regions 4.5 months after injection.[179]

Several rodent studies utilized engineered MSCs expressing tyrosine hydroxylase gene, vascular endothelial growth factor, or transduced to produce increased GDNF or cerebral dopamine neurotrophic factor showed mixed but overall positive results. [180–187] In a Rhesus monkey model of PD, vector-engineered umbilical cord-derived MSCs which showed neuronal differentiation were transplanted into the striatum resulting in recovery of behavior and neuroprotective effects.[188] Combined adipose-derived MSC delivery along with gene therapy delivering tyrosine hydroxylase and neurturin to the striatum in that monkey model showed better neuroprotective effects than gene therapy alone.[189]

In a rat nigrostriatal lesion model of PD the effects of human amniotic fluid stem cells and bone marrow derived mesenchymal stromal cells injected into the lesion site were assessed with a focus on bladder dysfunction. There was a temporary improvement of cystometry assessed bladder function in both stem cells groups compared to sham-treated rats.[190]

Only preliminary data are available on the use of MSCs in human PD. In an open-label study in 2010 and Indian researchers administered 10^6 autologous bone marrow-derived MSCs per

kilogram body weight unilaterally into the sublateral ventricular zone via stereotactic surgery in 7 patients with PD.[191] The procedure was well tolerated. 3 out of 7 patients were reported to have lasting improvement in the unified Parkinson's disease rating scale and other rating scales compared to baseline. The same group reported another open-label study in 2012 during which 8 PD and 8 "PD plus" patients received 2×10^6 allogeneic bone-marrow derived MSCs per kilogram body weight into the bilateral sublateral ventricular zone. [192] Improvement in unified Parkinson's disease rating scale and other measures was seen on follow-up, which was persistent in those with PD and transient in those with PD plus.

Future Directions in MSC Studies

Despite promising preclinical and early clinical findings, there continue to be many unanswered questions regarding the use of MSCs as a therapeutic approach in neurodegenerative disorders. Ultimately, the most important question is: do MSCs provide benefit to patients with neurodegenerative diseases? This efficacy question must be answered with well-designed clinical trials, which is a challenging task in neurodegenerative diseases. Within these clinical trials; however, we argue that it is equally important that biomarkers are investigated that can answer questions about MSC biology and their effects in the nervous system. Biomarker investigations into the immune system, neuroinflammation, growth factors, microRNA, EVs are examples of what need to be studied in human MSC clinical trials. Once we begin to more clearly understand *why* MSCs are beneficial in neurodegenerative diseases, we can rationally design future trials to optimize these therapies. As an example, if it is discovered that MSC efficacy correlates primarily with a specific effect on biomarker studies of neuroinflammation, the next set of experiments can be designed to maximize that effect. Variables that may be explored to optimize therapy should include dose, frequency, route of delivery, or autologous versus allogeneic therapy (some of which may be able to be answered in preclinical models). Furthermore, next-generation MSCs manipulated by gene therapy or specific culturing condition can then be developed specifically to alter that aspect of neuroinflammation. In this way, these novel MSC therapies not only can be properly validated, but also may reveal new mechanisms of MSC therapeutics that lead to further targeted drug development, which will be essential to move the field forward.

ABBREVIATIONS:

AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
BDNF	Brain-derived neurotrophic factor
EV	Extracellular vesicles
GDNF	Glial cell-derived neurotrophic factor
MSA	multiple system atrophy

MSC	mesenchymal stromal cell
PD	Parkinson’s disease
SOD-1	superoxide dismutatse-1

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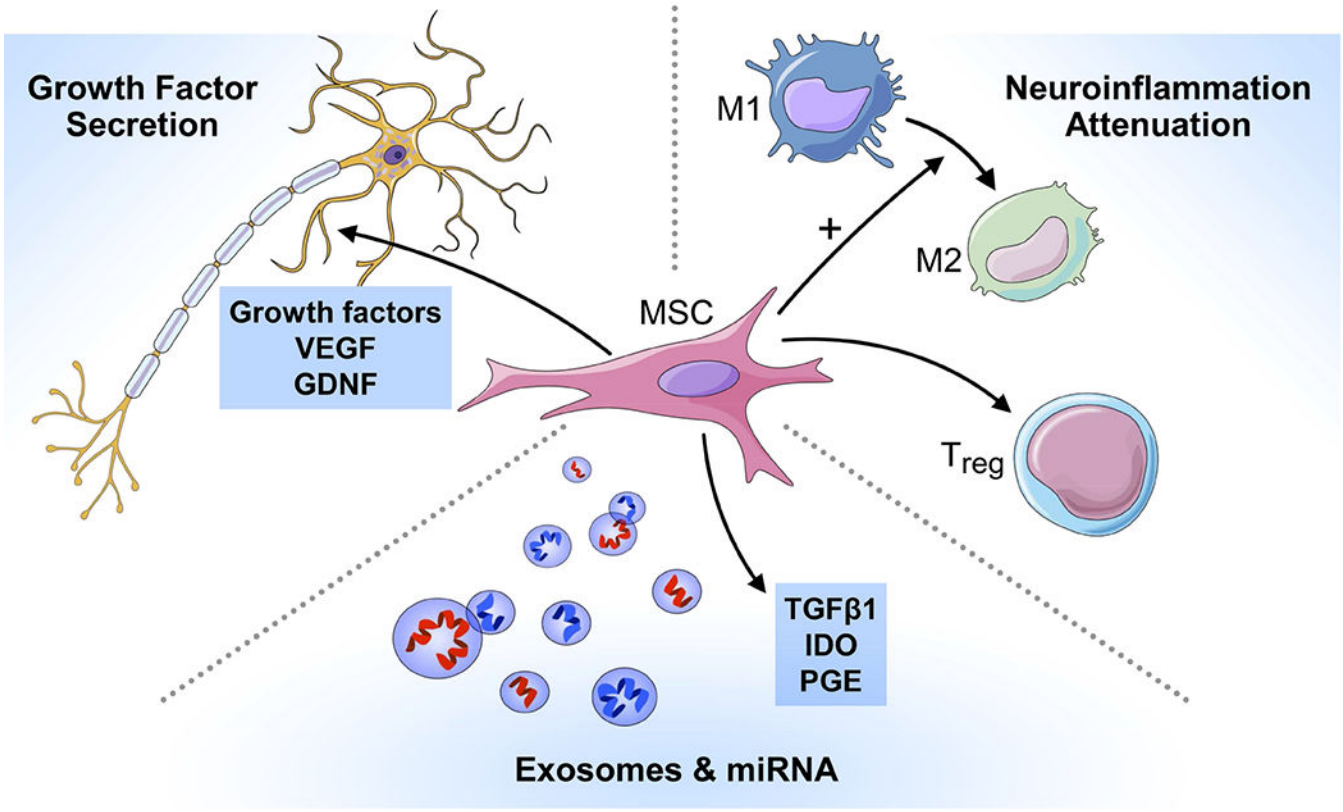

Figure.

Putative MSC mechanisms of action to treat neurodegenerative diseases: 1) growth factor secretion, 2) neuroinflammation attenuation, and 3) exosome and miRNA secretion. GDNF = glial cell-derived neurotrophic factor, IDO = Indoleamine-2,3-dioxygenase, miRNA = microRNA, PGE = prostaglandin, TGFB1 = transforming growth factor beta 1, Treg = Regulatory T cell, VEGF = vascular endothelial growth factor.

Table 1:

MSC-related studies listed at http://www.clinicaltrials.gov sorted by disease systems as of October 2018.

Disease Type	Number of Studies
Nervous System	218
Musculoskeletal	179
Immune System	177
Cardiovascular	140
Wounds/Injuries	133
Gastrointestinal	102
Genetic/Congenital	92
Endocrine	77
Urogenital	67
Respiratory Tract	57
Skin	53
Graft-versus-Host	45
Hematological	29
Infection	22

Table 2.

Clinical trials for the discussed neurological conditions that are registered with ClinicalTrials.gov and signified as “recruiting”, “enrolling by invitation”, “active not recruiting”, or “not yet recruiting” (as of October 2018).

Conditions	ClinicalTrials.gov#	Phase	Allo/Auto	MSC source	Site of Injection	Locations
Amyotrophic Lateral Sclerosis		1	Autologous	Bone Marrow	Intrathecal	Poland
		1	Allogeneic	Wharton’s Jelly	Intrathecal	Poland
		1	Autologous	Adipose	Intraspinal & Intrathecal	Poland
		1/2	Autologous	Bone Marrow	Intrathecal	Brazil
		1/2	Autologous	Adipose	Intravenous	Spain
		2	Autologous	Adipose	Intrathecal	USA
		3	Autologous	Bone Marrow	Intrathecal	USA
Alzheimer’s Disease		1	Allogeneic	Bone Marrow	Intravenous	USA
		1/2	Allogeneic	Umbilical Cord	Intracerebroventricular	South Korea
		1/2	Allogeneic	Umbilical Cord	Intravenous	China
		1/2	Autologous	Adipose	Intravenous	USA
		2	Allogeneic	Bone Marrow	Intravenous	USA
Multiple System Atrophy		1	Autologous	Adipose	Intrathecal	USA
		1	Autologous	Bone Marrow	Intracarotid	South Korea
Parkinson’s Disease		1	Allogeneic	Umbilical Cord	Intravenous	China
		1/2	Allogeneic	Bone Marrow	Intravenous	USA
		1/2	Allogeneic	Umbilical Cord	Intrathecal & Intravenous	Jordan

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