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Review

Stem cell-based therapies for neurological disorders

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Abstract: Cell-based therapies have been previously performed using fetal tissues for some central nervous system (CNS) disorders, such as Parkinson's disease. However, it can be difficult to collect a large number of cells for transplantation. Recent studies revealed that some stem cells can act as potential sources of cell-based therapies for degenerative and damaged areas in the CNS. In addition, stem cells can be used as cellular delivery vehicles for brain tumor because of tumor-tropic migratory capacity. Embryonic stem (ES) cells, mesenchymal stem cells (MSCs), and induced pluripotent stem (iPS) cells are the most attractive stem cells. iPS cells can be efficiently differentiated to neural stem cells and have the possibilities to overcome the ethical issues associated with ES cells. Therefore, cell-based therapies using iPS cells can be developed specifically for neurological disorders. In this article, we review the characteristics of ES cells, MSCs, and iPS cells as cell sources for stem cell-based therapies, and then discuss preclinical data and ongoing clinical trials for the CNS disorders.

Keywords: induced pluripotent stem cell; embryonic stem cell; mesenchymal stem cell; neural stem cell; neurological disorder; glioblastoma; Parkinson's disease; Alzheimer's disease

Abbreviations: Aβ: amyloid-β; ANG: angiopoietin; BBB: blood-brain barrier; BDNF: brain-derived neurotrophic factor; BFCN: basal forebrain cholinergic neurons; BTSCs: brain tumor stem cells; CD: cytosine deaminase; CNS: central nervous system; ES: embryonic stem; FACS: fluorescence activated cell sorting; FLAIR: fluid-attenuated inversion recovery; GABA: generated γ-aminobutyric acid; GCV: ganciclovir; GDNF: glial cell line-derived neurotrophic factor; GM-CSF: granulocyte macrophage-colony stimulating factor; GVHD: graft-versus-host disease; HGF: hepatocyte growth factor; HSV: herpes simplex virus; HSVtk: herpes simplex virus thymidine kinase; IL-2:

interleukin-2; INF: interferon; iPS: induced pluripotent stem; MSCs: mesenchymal stem cells; NGF: nerve growth factor; NK: natural killer; NSCs: neural stem cells; NT-ESCs: nuclear-transfer embryonic stem cells; TGF: transforming growth factor; TNF: tumor necrosis factor; TRAIL: TNF-related apoptosis-inducing ligand; VCAM-1: vascular cell adhesion molecule-1; VEGF: vascular endothelial growth factor; VLA-4: very late antigen-4; 5-FC: 5-flucytosine

1. Introduction

Axon regeneration in the mature mammalian central nervous system (CNS) is extremely limited. Myelin-, reactive glia-, and scar-derived CNS axon growth inhibitors (MAG and OMgp synergize with Nogo-A) and chondroitin sulfate proteoglycan family restrict axonal growth and neurological recovery. In addition, members of endogenous neural stem/progenitor cells are limited to in their ability to repair damaged CNS tissue [1–3]. Therefore, cell transplantation has been attracting attention in treating degenerative and damaged areas of CNS. In the past, cell-based therapies using midbrain dopamine neurons or cerebrocortical neurons have been already tried in Parkinson's disease and Alzheimer's disease patients [4]. However, it can be difficult to collect a large number of cells for transplantation.

According to recent researches, various stem cells have been shown to act as a possible source of cell-based therapy for the replacement of damaged CNS, and can secret neurotrophic factors for the tissue protection. Moreover, stem cells could be used as cellular delivery vehicles of cytokines, genes, or virus, because they possess tropic migratory capacity to the damaged area. Treatment strategy using stem cells as cellular delivery vehicles has also been used even for brain tumors [5,6].

Embryonic stem (ES) cells are able to differentiate into derivatives of the three embryonic germ layers [7]. Mesenchymal stem cells (MSCs) are also multipotent stem cells that have the potential to self-renew and differentiate into a variety of specialized cell types [8]. They can be easily harvested and expanded *in vitro* [8]. Induced pluripotent stem (iPS) cells are new type of pluripotent stem cells that can be generated from adult fibroblasts [9]. The iPS cells can overcome the immune rejection and ethical issues involved in ES cells in clinical applications [9].

Although the blood-brain barrier (BBB) is one of the main factors of some drugs (ex. chemotherapy) failure in CNS disease, stem cells are able to across the BBB like lymphocytes. MSCs exit in peripheral blood and integrate into the endothelial cells through the adhesion molecules such as vascular cell adhesion molecule-1(VCAM-1)/ very late antigen-4(VLA-4) and β1 integrin after contacting with the endothelial cells. MSCs were shown to be able to across the BBB through paracellular pathways, despite the presence of tight junctions [10,11]. Therefore, in addition to direct implantation, intravenous/arterial transfusion can be the possible way for stem cell-based therapy [10–12].

In this article, we review the characteristics of ES cells, MSCs, and iPS cells as cell sources for stem cell-based therapies (Table 1) and then discuss preclinical data and ongoing clinical trials for the CNS diseases; Parkinson's disease, Alzheimer's disease, Amyotrophic lateral sclerosis, Hungtington's disease, cerebral infarction, spinal cord injury, brain injury and brain tumor.

Table 1. Characteristics of stem cells.

Stem cells	Characteristics
ES cell	*Advantages* ・ infinite proliferating ・ multipotency ・ capacity for neural replacement function *Disadvantages* ・ ethical concern (blastocyst) ・ difficulty to use autologous grafts ・ risk of immune rejection (allogeneic cell transplantation) ・ risk of teratoma formation
MSC	*Advantages* ・ easily harvested from the adult tissue (Autologous grafts can be used.) ・ preventing immune rejection ・ low risk of teratoma formation *Disadvantages* ・ limited long-term engraftment ・ limited capacity of differentiation ・ difficulty to maintain the differentiation capacity after multiple passages ・ weak neural replacement function
iPS cell	*Advantages* ・ easily harvested from the adult tissue (Autologous grafts can be used) ・ infinite proliferating ・ multipotency ・ capacity for neural replacement function *Disadvantages* ・ risk of teratoma formation (Recently iPS cells can be established without c-myc) ・ chromosomal insertion by viral vector (An episomal vector prevent chromosomal insertion) ・ risk of immune rejection (allogeneic cell transplantation)

1.1. ES cells

ES cells are pluripotent stem cells derived from the undifferentiated inner cell mass of a blastocyst. Isolating the inner cell mass results in the destruction of the blastocyst. They can differentiate into all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. It has high telomerase activity that can divide persistently. Because of their plasticity and self-renewal capacity, ES cell therapies have been proposed for regenerative medicine and tissue replacement after injury or disease. Other potential uses of ES cells include research of genetic diseases and toxicology testing [7].

There is a problem of graft-versus-host disease (GVHD) associated with allogeneic cell transplantation, as well as ethical concerns. Therefore, immunosuppressive drugs are necessary to prevent GVHD. These problems may be solved using autologous donors [13]. However, autologous grafts are unsuitable for acute diseases.

The established marker for mouse ES cells is SSEA-1. The markers for human ES cells are SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81 [14]. Transplantation of ES cells themselves have a risk of tumor formation, comprising all three germ layers, resembling spontaneous teratomas. Prior to transplantation, cells expressing pluripotency-associated cell surface markers described above should be eliminated by fluorescence activated cell sorting (FACS) to prevent teratoma formation [15].

1.2. MSCs

MSCs are prototypical adult stem cells with capacity for self-renewal and differentiation to various tissues (mesoderm- and nonmesoderm-derived tissues). The minimum criteria of MSCs include: remain plastic-adherent under standard culture conditions; express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR; differentiate into osteoblasts, adipocytes, and chondrocytes *in vitro*. Recently, MSCs were shown to be differentiated to endocapillary cells, myocardium, skeleton muscle, liver cells, glial cells, insulin producing cells, and epithelial cells [16].

MSCs can be harvested from fetal Wharton's jelly, adult bone marrow, synovialis, fatty tissue, placenta, heart and liver [8]. From a therapeutic perspective, and facilitated by the ease of preparation, MSCs are also s promising therapeutic tool for CNS disorders. MSCs can be harvested by patients themselves; therefore, MSCs do not suffer from immune rejection and ethical issues [17,18].

MSCs themselves do not develop teratoma compared with ES cells [19]. However, MSCs proliferate in hetero-generous populations that correlate to different cellular functions. To improve purity, FACS can be used to sort cells labeled with cell surface markers [20,21]. In addition, cell function might be changed from original ones, because cell state reprogramming is not normal in MSCs. Long-term cultivation of MSCs as a monolayer is known to result in a reduction of their functionality and viability [19].

MSCs secrete trophic factors like brain-derived neurotrophic factor (BDNF) in response to autocrine interferon (IFN)-β. In addition, nerve growth factor (NGF), and glial cell line-derived neurotrophic factor (GDNF), as well as angiogenic vascular endothelial growth factor (VEGF) and angiopoietin (ANG)1 were shown to be secreted by MSCs in many other experiments [16].

Immunosuppressive drugs are not needed for transplantation, because MSCs have immunomodulatory function, leading to prevent GVHD. MSCs inhibit the proliferation and/ or functions of CD4(+) Th1 and Th17 cells, CD8(+) T cells, and natural killer cells predominantly via the secretion of Transforming Growth Factor (TGF)-β1 and hepatocyte growth factor (HGF) [22–24]. In other reports, autologous and allogeneic expanded human MSCs have been utilized to treat acute GVHD. It was associated with the direct inhibition of donor CD4(+) T cell proliferation and reduction of human tumor necrosis factor (TNF)-α in serum [25,26].

However, there are unsolved problems for stem cell-based therapy using MSCs. Von Bahr et al. suggested autopsy specimens after MSCs transplantation showed limited long-term engraftment and no ectopic tissue formation of MSCs [27,28]. MSCs could not have the neural replacement function. The functional recovery mediated by MSCs might be caused by the neurotrophic factors.

In addition, MSCs cannot be efficiently differentiated into the nervous tissue. Therefore, neural stem cells differentiated from ES cells or iPS cells might be appropriate for treatment of neurological disorders [27,28].

1.3. iPS cells

iPS cells were established from mouse and human tissue in 2006 and 2007 respectively. The iPS cells can be generated directly from adult cells using retroviral or lentiviral vector and are established by introducing four types of genes (*Oct3/4, c-myc, Sox2, Klf4*) to fibroblasts harvested from mouse and human skin [9,29]. The most established marker of mouse and human iPS cells are similar to ES cells [29]. Johannesson et al. suggested comparable frequencies of coding mutations and loss of imprinting in human iPSCs. The occurrence of genetic and epigenetic defects in both human nuclear-transfer embryonic stem cells (NT-ESCs) and human iPS cells suggests that they are inherent to reprogramming, regardless of derivation approach [30,31].

Recently, an episomal vector was used for the transduction to prevent chromosomal insertion that cannot be accomplished by viral and plasmid vectors [3,32,33]. In addition, iPS cells can be cultured under the feeder-free condition, and laminin-511 supports the stable culture of iPS cells. It has been also found that iPS cells can be established without *c-myc*, which leads to being able to prevent canceration [11,34,35]. The efficiency to culture iPS cells has been rapidly improved [29,36–38].

The iPS cells hold great promise in the field of CNS disorders. Generating ES cells involves manipulating the pre-implantation stage embryo. In addition, it is difficult to create patient-matched ES cell lines. Since iPS cells can be derived directly from adult tissues, they can be established by patients themselves, which leads to the transplantation without the risk of immune rejection. Morizane et al. demonstrated the advantages of autologous transplantation compared to the allogeneic transplantation of dopamine-producing cells derived from iPS cells in the brain [39]. This research suggested that autologous transplantation has advantageous in minimizing the immune response by microglia and T cells in the brain compared to the allogeneic grafts [39]. However, autologous grafts are unsuitable for acute diseases, such as spinal injury and cerebral infarction, because to prepare autologous grafts, a long period and significant efforts are required. Stem cell banks for allogeneic transplantation are also needed as with ES cells. The building of iPS cells stock for regenerative medicine involves the collection of cells from healthy donors with homozygous HLA to reduce the risk of GVHD. The aim of the stock is to hold iPS cells of guaranteed quality which can be supplied quickly to medical care institutions and research institutions when required [40]. The iPS cells can be also used in personalized drug discovery efforts and understanding the patient-specific basis of disease [3,41].

A novel method of highly efficient neural conversion of human ES and iPS cells was established by dual inhibition of SMAD1/5/8 and SMAD2/3 signaling using SB431542 and Noggin inhibitors. This novel protocol allows for the derivation of relevant neuron subtypes after much shorter differentiation periods compared with stromal feeder mediated induction protocols [42].

2. Recent studies

2.1. Parkinson's disease

2.1.1. Preclinical study

Parkinson's disease is a long-term degenerative disorder due to the loss of brain. Dopaminergic neurons derived from human ES or iPS cells were transplanted into the striatum of rat and monkey Parkinson's disease models. Excellent dopamine-producing neuron survival, and improved function without any tumor formation were shown, which indicated the development of stem cell-based therapies in Parkinson's disease [43–45]. Grealish et al. compared the growth and function of human ES cell-derived dopaminergic neurons and human fetal mesencephalic neurons for rodent models of Parkinson's disease. There were no differences in engraftment and function following transplantation [46,47].

Autologous engraftment of dopaminergic neuron-like cells derived from MSCs of parkinsonian macaques showed long-term survival of transplanted cells and improved motor function. Transplantation of differentiated autologous MSCs may also represent a safe and effective cell-based therapy for Parkinson's disease [48].

The iPS cell-derived dopaminergic neurons from skin fibroblasts of patients with Parkinson's disease demonstrated long-term survival of transplanted cells and functional effects in a rat animal model of Parkinson's disease [49,50]. Recently, this research was first applied using human iPS cells for the primate model of Parkinson's disease [51]. Functional effects and safety without forming any tumors for 2 years were demonstrated [51].

2.1.2. Clinical study

Clinical use of allografts of fetal mesencephalic tissue for replacing dopaminergic neurons in patients with Parkinson's disease was first achieved in 1987 [52]. However, it has ethical considerations to use fetal tissue as a source of stem cells. It is also difficult to obtain enough cell volume for transplantation. Therefore, ES cells, MSCs, and iPS cells have attracted attention.

A pilot phase I clinical trial was conducted in 2015 using allogeneic bone marrow-derived MSCs therapy for idiopathic Parkinson's disease (NCT02611167). The purpose of this study is to assess the safety, feasibility, and efficacy of intravenous allogeneic bone marrow-derived MSCs therapy. In 2017, a phase I/II clinical trial started to assess the safety and efficacy of stereotactically striatum transplantation of human ES cell-derived neural precursor cells in patients with Parkinson's disease (NCT03119636). In 2018, a clinical trial using human iPS cell-derived neural stem cells is planned for treating patients with Parkinson's disease (Table 2).

Table 2. Ongoing and planning clinical trials.

ID	Phase	Cell	Disease	Age	Enrollment	Completion date	Dose	Intervention	Patient conditioning
NCT03119636	I/II	ES cells-derived NSCs	Parkinson's disease	50–80	50	December, 2020	N/A	stereotactically implanted in the striatum	・Hoehn and Yahr Stage 3 or 4 in the off state ・a history over 5 years ・dopamine is effective or once ・without immunosuppressant drugs
NCT02611167	I	Bone marrow-derived MSCs	Parkinson's disease	45–70	20	November, 2019	1,3,6,10 $\times 10^6$ /kg	intravenous	・a modified Hoehn and Yahr stage of 3 or less in the levodopa OFF state ・diagnosis of PD between 4 to 7 years. ・a stable Parkinson's disease symptomatic therapy for at least 90 days prior to screening ・without immunosuppressant drugs
planning	I/II	iPS cells-derived cells	Parkinson's disease	N/A	N/A	N/A	N/A	N/A	N/A
NCT02833792	II	MSCs	Alzheimer's disease	55–80	40	June, 2018	1.5 $\times 10^6$ /kg	intravenous	・diagnosed with mild to moderate dementia for at least 3 months prior to enrollment ・Mini Mental State Examination between 12–24 ・without immunosuppressant drugs

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ID	Phase	Cell	Disease	Age	Enrollment	Completion date	Dose	Intervention	Patient conditioning
NCT02600130	I	Bone marrow-derived MSCs	Alzheimer's disease	50–80	30	October, 2019	2×10^7, 1×10^8	intravenous	▪ score between 18 and 24 on the Mini Mental State Examination ▪ be using an acetylcholinesterase inhibitor and/or Memantine treatment for at least 4 months ▪ without immunosuppressant drugs
NCT02054208	I/IIa	Umbilical cord blood-derived MSCs	Alzheimer's disease	50–85	45	July, 2019	1 or 3 × 10^7	Ommaya Reservoir	▪ diagnosis of Probable Alzheimer type according to NINCDS-ADRDA criteria ▪ without immunosuppressant drugs
NCT03268603	II	Adipose-derived MSCs	Amyotrophic Lateral Sclerosis	Over 18	60	December, 2019	1×10^8	intrathecal	▪ history of a chronic onset of a progressive motor weakness of less than two years duration ▪ riluzole-naïve subjects are permitted ▪ without immunosuppressant drugs
NCT02290886	I/II	Adipose-derived MSCs	Amyotrophic Lateral Sclerosis	Over 18	40	February, 2021	1,2 or 4 $\times 10^6$/kg	intravenous	▪ more than 6 and less than 36 months of evolution of the disease ▪ possibility of obtaining, at least, 50gr of adipose tissue ▪ treatment with riluzole, for at least, a month before the inclusion ▪ without immunosuppressant drugs

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ID	Phase	Cell	Disease	Age	Enrollment	Completion date	Dose	Intervention	Patient conditioning
NCT03186456	I	Umbilical cord blood-derived MSCs	Cerebral infarction	40–75	40	May, 2018	0.5 or 1 $\times 10^6$ /kg	intravenous	▪ within 2 weeks onset of symptoms. ▪ receive basic treatment with Aspirin Enteric-coated Tablets ▪ without immunosuppressant drugs
NCT03176498	I/II	Umbilical cord blood-derived MSCs	Cerebral infarction	20–75	40	February, 2018	N/A	intravenous	▪ receive basic treatment with Aspirin Enteric-coated Tablets and Atorvastatin Calcium ▪ without immunosuppressant drugs
NCT02481440	I/II	Umbilical cord blood-derived MSCs	Spinal cord injury	18–65	44	December, 2018	1 × 10^6/kg	Intrathecal	▪ American Spinal Injury Association Impairment Scale A-D ▪ time between injury and enrollment greater than 2 weeks ▪ without immunosuppressant drugs
NCT02574572	I	Bone marrow-derived MSCs	Spinal cord injury	18–65	10	June, 2020	N/A	Laminectomy and transplantation	▪ at least 12 months of injury ▪ ASIA grade A ▪ at cervical level, between C5 and C7 ▪ without immunosuppressant drugs
planning	I/II	iPS cells-derived cells	Spinal cord injury	N/A	N/A	N/A	N/A	N/A	▪ patients in the sub-acute stage of spinal cord injury ▪ with immunosuppressant drugs

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ID	Phase	Cell	Disease	Age	Enrollment	Completion date	Dose	Intervention	Patient conditioning
NCT02210624	I	Bone marrow-derived MSCs	Brain injury	18–75	4	December, 2018	1ml/10kg	Intrathecal	▪ 7 points less than Glasgow coma scale ▪ 14 days after the event occurs in an oxygen-free brain injury patients ▪ without immunosuppressant drugs
planning	I/II	Bone marrow-derived MSCs	Brain injury	N/A	N/A	N/A	N/A	N/A	▪ patient in the chronic stage of brain injury
NCT01172964	I	an immortalized, clonal human NSC line with CD	Brain tumor	Over 13	15	Completed (November, 2017)	N/A	Surgery and transplantation	▪ histologically-confirmed, diagnosis of a grade III or grade IV glioma ▪ recurred or progressed after chemoradiation ▪ without immunosuppressant drugs
NCT03252535	II	MSCs (Cellavita HD)	Huntington's disease	21–65	35	April, 2020	1 or 2 × 10^6 /kg	Intravenous	▪ a score of 5 points or higher for the motor evaluation of the UHDRS scale ▪ without immunosuppressant drugs

CD: cytosine deaminase; ES: Embryonic stem; MSC: mesenchymal stem cell; NSC: neural stem cell; N/A: not available; iPS: Induced pluripotent stem; UHDRS: Unified Huntington's Disease Rating Scale.

2.2. Alzheimer's disease

2.2.1. Preclinical study

Alzheimer's disease is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, which cause memory dysfunction and neurodegeneration. After transplantation of human ES cells into the hippocampus of mice with a destroyed basal forebrain, medial ganglionic eminence-like progenitors derived from human ES cells produced basal forebrain cholinergic neurons (BFCNs) that synaptically connected with endogenous neurons [53]. In addition, these progenitors generated γ-aminobutyric acid (GABA) neurons, which led to improved memory [53].

Human bone marrow-derived MSCs were transplanted into the hippocampus of an Alzheimer's disease mouse model, reducing Aβ deposition in the brain [54]. Moreover, reducing Aβ -induced oxidative stress and memory improvement were observed, which supported the beneficial role of MSCs in treating Alzheimer's disease [54]. Human umbilical cord blood-derived MSCs was injected intravenously into an Alzheimer's disease mouse model, which promoted the survival of cholinergic neurons in the frontal lobe, and showed cognitive rescue with improved memory function [55]. Positron emission tomography also showed the increased uptake of fluorodeoxyglucose [55].

Human iPS cell-derived macrophage-like cells expressing Neprilysin-2, a protease with Aβ-degrading activity, were intracerebrally administered into an Alzheimer's disease mouse model, leading to significantly reduced Aβ in the brain interstitial fluid [56].

2.2.2. Clinical study

Three clinical trials (Phase I from 2014, Phase I/IIa from 2015, and Phase II from 2016) have been conducted for Alzheimer's disease to assess the safety and tolerability of allogeneic human MSCs intraventricularly or intravenously to patients with dementia due to Alzheimer's disease (NCT02054208, NCT02600130, and NCT02833792) (Table 2).

2.3. Amyotrophic lateral sclerosis

2.3.1. Preclinical study

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease that affects neurons in the brain and spinal cord. Amyotrophic lateral sclerosis is characterized by stiff muscles, and muscle twitching, resulting in difficulties in speaking, swallowing, and breathing. Transplantation of human ES cell-derived motor neuron progeny into a rat amyotrophic lateral sclerosis model resulted in engraftment, maintenance of motor neuron, and axonal projections caused by the choline acetyltransferase positive fibers [57]. In other reports, transplanted human ES cell-derived motor neurons also enhanced the host neuron survival and motor function in an amyotrophic lateral sclerosis mouse model [58,59].

Glial-restricted precursors secreting neurotrophic factors derived from human MSCs were transplanted around the cervical spinal cord respiratory motor neuron pools in an amyotrophic lateral

sclerosis rat model, leading to prolonged overall survival [60].

Recent research pioneered the ability to generate a nerve organoid composed of a fascicle of axons extended from a spheroid of human iPS cell-derived motor neurons [61]. This nerve organoid will be applicated to patients with amyotrophic lateral sclerosis in the future [61].

2.3.2. Clinical study

A multicenter phase I/II clinical trial was conducted to evaluate the safety of intravenously administering autologous MSCs from adipose tissue in patients with amyotrophic lateral sclerosis in 2014 (NCT02290886). In 2017, a phase II clinical trial was started using intrathecal autologous adipose-derived MSCs for treatment of amyotrophic lateral sclerosis (NCT03268603). The purpose of this study is to determine the safety and efficacy of intrathecal treatment delivered to the cerebrospinal fluid of MSCs in amyotrophic lateral sclerosis patients every 3 months for a total of 4 injections over 12 months (Table 2).

2.4. Hungtington's disease

2.4.1. Preclinical study

Huntington's disease is an inherited disease that causes the progressive breakdown (degeneration) of nerve cells in the brain. From 2000s, stem-cell based therapy has been tried for animal models of Huntington's disease. Human ES cells-derived striatal progenitors showed differentiation into striatal neurons following xenotransplantation into adult rats. Long-term proliferation of human striatal progenitors leads to xenograft overgrowth in the rat brain [62]. Human adipose-derived MSCs transplantation showed striatal degeneration and behavioral deterioration in R6/2 transgenic model mice of Hungtington's disease, possibly via secreted neurotrophic factors [63]. There were no reports using iPS cells as the source of stem cell-based therapy for Huntington's disease. iPS cells were used as a cellular disease model system to understand the pathogenesis and neurodegeneration mechanisms in Huntington's disease [64].

2.4.2. Clinical study

From 1990s, cell based therapy using human fetal striatal transplantation was conducted for the patients of Huntington's disease. Transplanted striatal cells have improved behavioral signs in the patients of Huntington's disease. However, these effects were controversial because some patients could not have the advantages from transplanted striatal cells [65,66]. Keene et al. highlights the potential for graft overgrowth in a patient who received the intrastriatal human fetal neural transplants for the first time. They suggested specific microenvironment in the patients of Huntington's disease might be associated with teratoma formation after the fetal neural transplants. Further investigations are needed [67].

The stem cell-based therapy of Cellavita HD was developed for Huntington's disease using MSCs. A phase II clinical trial aimed to evaluate the dose-response evaluation of the intravenous administered Cellavita HD product in patients with Huntington's disease in 2017 (NCT03252535) (Table 2).

2.5. Cerebral infarction

2.5.1. Preclinical study

A cerebral infarction is occupied by necrotic tissue in the brain resulting from an occlusion in the arteries supplying blood and oxygen to the brain. An ischemic stroke typically presents a rapid onset of neurological deficit. Transplanted neural stem cells (NSCs) derived from mouse ES cells showed to engraft and migrate to ischemic area followed by expression of neuronal and glial markers [68]. Primate ES cell-derived neuronal progenitors transplanted into mouse ischemic brain also showed the survival and differentiation, as well as network formation [69].

Chen et al. have demonstrated that there is no decrease in the histopathological infarction size; however, intravenously injected MSCs migrated into the infarction core in the rat middle cerebral artery occlusion model [70,71]. Functional MRI showed an activated motor cortical area after following transplantation [71]. Real-time polymerase chain reaction evaluated the expression of neurotrophic factors like HGF, NGF and GDNF in rat bone marrow derived MSCs [72]. Human MSCs with the GDNF gene was intravenously infused into the rat middle cerebral artery occlusion model [5,73]. MRI and behavioral analyses revealed that GDNF-human MSCs showed improved recovery from ischemia [5,73]. ANG-1 gene-modified human MSCs were also intravenously infused into a rat model of middle cerebral artery occlusion [74]. Infused cells improved angiogenesis near the ischemic lesions, neovascularization, and regional cerebral blood flow [74]. However, MSCs could not enhance endogenous neurogenesis and functional recovery in a murine model of chronic ischemic infarction (not subacute infarction). The functional recovery in subacute stage of cerebral infarction mediated by MSCs might be caused by the only neurotrophic factors. In contrast, ES cells and iPS cells have the possibility to have neural-replacement effect even for chronic cerebral infarction [75,76].

Astroglial-like and neuron-like cells derived from human iPS cells could improve motor function, reduce infarction size, decrease inflammation cytokines, and mediate neuroprotection in the rat middle cerebral artery occlusion model [70]. Hermanto et al. developed the feeder-free condition for differentiation cortical neurons from human iPS cells [77]. These iPS cells demonstrated polarized reactivity for the ischemic area in the rat ischemic model [77].

2.5.2. Clinical study

Some clinical trials have been previously conducted using autologous MSCs. An open study supported the feasibility and safety of intravenously transplanted autologous human MSCs in 12 stroke patients with ischemic grey matter, white matter and mixed lesions in 2011 [78]. High intensity lesion on fluid-attenuated inversion recovery (FLAIR) significantly decreased after transplantation. The neurological deficit was significantly improved in 11 of 12 patients. This result seemed to be caused by growth and trophic factors, such as BDNF and angiogenic stimulation factor including vascular endothelial growth factor and angiopoietin-1 from administered MSCs [78]. A phase I/IIa clinical trial has been performed using bone marrow-derived MSCs (SB623) in 2016, which indicated no dose-limiting toxicities or deaths. Although the values for the European Stroke Scale and National Institutes of Health Stroke Scale significantly decreased, no changes were observed in the values for the modified Rankin Scale [79].

The phase I clinical trial conducted in 2017 aimed to determine the safety and efficacy of treating acute ischemic stroke patients with intravenously administered human umbilical cord MSCs (NCT03186456). Another phase I/II clinical trial conducted in 2017 using human umbilical cord MSCs which is intravenously infused also targeted cerebral infarction patients (NCT03176498). A phase III clinical trial was conducted using autologous MSCs, which is intravenously infused to the patient with subacute atherothrombotic cerebral infarction from 2013 in Japan (Table 2).

2.6. Spinal cord injury

2.6.1. Preclinical study

A spinal cord injury is a damage to the spinal cord that causes changes in its function, either temporary or permanent. Mouse ES cell-derived gliogenic NSCs were effective in promoting recovery from the subacute phase in a rat spinal cord injury model [34,80]. Gait analysis demonstrated that transplanted rats showed hindlimb weight support and partial hindlimb coordination [34,80]. Secondary neurospheres (not first neurospheres) that can be differentiated into both neuronal and glial cells were more effective for the spinal cord injury [34,80].

Transplantation of human ES cell-derived oligodendrocyte progenitor cells into an adult rat spinal cord injury model enhanced remyelination and promoted motor function improvement [81,82]. Intravenously administered rat MSCs derived from bone marrow improved functional outcomes in spinal cord injury, including improved locomotor recovery [83]. There was extensive remyelination of the injuried area and increased sprouting of the corticospinal tract and serotonergic fibers after intravenous MSCs infusion in the rat models of spinal cord injury [84].

Tsuji et al. demonstrated grafted 38C2 murine iPS-secondary neurospheres differentiated into neurons, astrocytes, and oligodendrocytes without forming teratomas and promoted functional recovery in a mouse spinal cord injury model [85]. However, they speculated that teratoma formation and subsequent deterioration of function recovery would occur in the other type of mouse iPS cells (256H13) [85]. Therefore, pre-evaluated of transplanted iPS cells was needed to remove the “unsafe” clone which induce teratoma formation. Neuroepithelial-like stem cells derived from human iPS cells could differentiate into NSCs in the mouse spinal cord injury model and promote functional recovery of hind limb motor function without any tumor formation [86,87]. Transplanted human iPS cell-derived NSCs enhanced axonal regrowth and angiogenesis, as well as prevented demyelination without any tumor formation in a primate model of spinal cord injury [88]. This was the first report for primate model (common marmoset) of spinal cord injury.

The transplantation of NSCs at the chronic phase of spinal cord injury could not promote functional recovery. A more prominent glial scar was located around the lesion epicenter enclosed the grafted cells in the chronic phase of spinal cord injury. Furthermore, the infiltration of M2 macrophages, was significantly higher at the sub-acute phase than the chronic phase. Therefore, to achieve functional recovery in cases at the chronic phase, modification of the microenvironment of the injured spinal cord focusing on glial scar formation and inflammatory phenotype should be considered [89].

2.6.2. Clinical study

A phase I clinical trial using oligodendrocyte progenitor cells derived from human ES cells was performed in patients with subacute complete thoracic spinal cord injuries by Geron Corporation. The phase I/II clinical trial had already been performed to assess the safety and therapeutic efficacy of autologous human bone marrow cells transplantation and the administration of granulocyte macrophage-colony stimulating factor (GM-CSF) for 35 patients with complete spinal cord injury. The results revealed that bone marrow cell transplantation and GM-CSF administration were not associated with any serious adverse clinical events that increased morbidities [90,91].

A phase I clinical trial commenced in 2015, with the aim to analyze the safety and efficacy of autologous bone marrow MSCs transplantation after the laminectomy in patients with cervical chronic and complete spinal cord injury (NCT02574572). In addition, a phase I/II clinical trial aimed to evaluate the safety and efficacy of intrathecal administration of allogeneic umbilical cord-derived MSCs to patients with spinal cord injury in 2015. In 2018, a clinical trial using human iPS cell-derived neural stem cells is planned for treating patients with sub-acute spinal cord injury in Japan (Table 2).

2.7. Brain injury

2.7.1. Preclinical study

Traumatic brain injury is typically caused by an external mechanical force. Murine ES cell-derived NSCs transplanted into injured rat brains enabled functional recovery with significant improvement in the rotarod test and in the composite neuroscore test when compared with the control group [92]. Transplanted MSCs perform endogenous repair through cell replacement and secretion of trophic factors. MSCs exhibited the ability to build a biobridge between the neurogenic niche and the site of injury during the repair phase of traumatic brain injury [93,94].

2.7.2. Clinical study

A pilot trial was conducted in 2014 to evaluate the safety and efficacy of autologous intrathecal bone marrow-derived MSCs therapy in patients with brain injury (NCT02210624). SanBio Company engineered the modified bone marrow derived MSCs (SB623) for a patient with chronic stroke. The SB623 cells were deemed safe with improved clinical outcomes [79]. A clinical trial for the use of SB623 cells in the treatment for the patient with chronic brain injury will be conducted in Japan (Table 2).

2.8. Brain tumor

2.8.1. Preclinical study

Glioblastoma is the most aggressive brain tumor [95]. It is incurable by the conventional standard therapy (maximal safe tumor resection, adjuvant chemotherapy and irradiation), because brain tumor stem cells (BTSCs) has features of infiltrative growth and resistance to irradiation and

tumoricidal agents. Therefore, both glioma cells and BTSCs must be treated to improve tumor control [96].

Gene therapies, such as cytokine-based, suicide gene, and oncolytic virus therapies, were expected treatments [97]. Although some gene therapies using viral vectors were conducted as clinical trials, they could not achieve ideal results [98]. Viral vectors could not be enough to cover the large invasion area of malignant glioma. Therefore, stem cells can be possible cellular delivery vehicles of cytokines, suicide genes, or oncolytic virus to tackle glioma cells [6].

Nakamura et al. first used rat MSCs as a cellular delivery vehicle for rat malignant glioma model in 2004, transplanting genetically-modified MSCs infected with an adenoviral vector encoding human interleukin-2 (IL-2) [99]. MSCs migrated to contralateral glioma cells, thus prolonging survival [99,100]. IL-23-expressing bone marrow-derived neural stem-like cells could effectively induce antitumor immunity against mouse glioma model [101]. CD8(+) T cells are critical for antitumor activity, and CD4(+) T cells and natural killer (NK) cells were also involved [101]. The tumor-specific therapeutic effect of TNF-related apoptosis-inducing ligand (TRAIL)-producing human umbilical cord blood-derived MSCs also significantly inhibited tumor growth and prolonged the survival of glioma mouse model [102].

The use of oncolytic adenovirus-loaded human bone marrow-derived MSCs showed improved delivery of adenovirus, enhanced dissemination of sarcomatous tumor, and increased persistence of viruses via suppression of the antiviral immune response [103]. NSCs with conditionally replicating herpes simplex virus (HSV) type 1 and adenovirus had the potential to expand the range of delivery of HSV-1 vectors to tumor cells in the brain [104,105].

Some well-known combinations of suicide genes and prodrugs are herpes simplex virus thymidine kinase (HSVtk) + ganciclovir (GCV) and cytosine deaminase (CD) + 5-flucytosine (5-FC) [106]. Some reports showed that suicide gene therapy with HSVtk or CD using human NSCs as cellular delivery vehicle could significantly prolong survival in brain tumor mouse models [107,108]. MSCs with HSVtk or CD also showed the antitumoral effects toward a mouse malignant glioma model. Both NSCs and MSCs could migrate evenly to the contralateral tumor [109,110]. Mouse iPS cell-derived NSCs with HSVtk have been previously reported and showed equivalent results as described above. Until now, the study using human iPS cell-derived NSCs has not been reported [111].

In brain tumor, NSCs might be considered as the most effective cellular vehicle because of their affinity to the brain. NSCs cannot be efficiently differentiated from MSCs. Long-term engraftment was not also easy for MSCs [28].

2.8.2. Clinical study

A pilot trial using NSCs with CD was recently completed, but the results are not yet available (NCT 01172964). It is a pilot feasibility study of oral 5-FC and genetically-modified NSCs expressing E. Coli CD (Food and Drug Administration approved HB1.F3.CD NSCs) for treating recurrent high-grade gliomas (Table 2). There have been several clinical trials using stem cells as the cellular delivery vehicle for malignant glioma. iPS cells are attractive tools because a large amount of NSCs could be efficiently differentiated from iPS cells. Emergences of iPS cells have the possibility to accelerate gene therapy using NSCs as cellular delivery vehicles for malignant glioma.

3. Future directions

Stem cells have the ability to undergo self-renewal and to differentiate into various types of cells. In addition, some stem cells can secret neurotrophic factors for the tissue protection, and can migrate to the damaged area for tissue repairing. They could be also used as cellular delivery vehicles of cytokines, genes, or virus [6,12]. Therefore, stem cell-based therapy is a promising approach.

There were many preclinical/clinical studies using MSCs, because MSCs are easily harvested from adult tissues, can prevent immune rejection, and have low risk of teratoma formation. However, there are unsolved problems using MSCs especially for neurological disorders. The functional recovery mediated by MSCs might be caused by the only neurotrophic factors [27,28]. In addition, MSCs cannot efficiently differentiate into the nervous tissue [6]. Therefore, neural stem cells differentiated from ES cells or iPS cells can be appropriate for neurological disorder.

A comparative analysis on which type of stem cell is appropriate for the neurological disorders is needed. Although technical hurdles such as optimal dose, differentiation state, mode of administration, and potential therapeutic mechanisms still need to be studied, stem cells show potential in curing human neurological disorders.

Conflict of interest

All authors declare no conflicts of interest in this paper

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