REVIEW

Stem cells: a promising candidate to treat neurological disorders

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Abstract

Neurologic impairments are usually irreversible as a result of limited regeneration in the central nervous system. Therefore, based on the regenerative capacity of stem cells, transplantation therapies of various stem cells have been tested in basic research and preclinical trials, and some have shown great prospects. This manuscript overviews the cellular and molecular characteristics of embryonic stem cells, induced pluripotent stem cells, neural stem cells, retinal stem/progenitor cells, mesenchymal stem/stromal cells, and their derivatives *in vivo* and *in vitro* as sources for regenerative therapy. These cells have all been considered as candidates to treat several major neurological disorders and diseases, owing to their self-renewal capacity, multi-directional differentiation, neurotrophic properties, and immune modulation effects. We also review representative basic research and recent clinical trials using stem cells for neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and age-related macular degeneration, as well as traumatic brain injury and glioblastoma. In spite of a few unsuccessful cases, risks of tumorigenicity, and ethical concerns, most results of animal experiments and clinical trials demonstrate efficacious therapeutic effects of stem cells in the treatment of nervous system disease. In summary, these emerging findings in regenerative medicine are likely to contribute to breakthroughs in the treatment of neurological disorders. Thus, stem cells are a promising candidate for the treatment of nervous system diseases.

Key Words: *nerve regeneration; stem cells; transplantation; stem cell therapy; nervous system; neurodegenerative disease; neurological disorders; animal experiment; clinical trial; regenerative medicine; neural regeneration*

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Introduction

The central nervous system is considered to be the most sophisticated and less understood system in the human body. Disorders or diseases of the central nervous system, such as Alzheimer's disease (AD) and Parkinson's disease (PD), usually lead to deterioration and irreversible impairment of the structures and functions of nervous tissue, which is often accompanied by serious cognitive or physical loss in affected patients. Apart from the limited potential of endogenous regeneration in the central nervous system, therapies for such disorders are largely symptomatic and pharmaceutical, thus possessing inherent disadvantages of temporary efficacy or overwhelming cost (Lindvall and Kokaia, 2006). Therefore, it is urgent to find effective ways to cope with damage associated with central nervous system disorders or diseases. Stem cell therapy is a promising candidate to treat neurological disorders, and the rationale and feasibility of stem-cell-based therapies have been verified during recent years.

Neural stem cells (NSCs) are the origin of various types of neurons, astrocytes, and oligodendrocytes during embryonic development of the central nervous system and subsequently exist primarily in the subventricular zone (SVZ) and subgranular zone (SGZ) of the hippocampal dentate gyrus in the adult mammalian brain (Lim and Alvarez-Buylla, 2014). Their capacity for self-renewal and the ability to generate various neural cell types make NSC transplantation therapy a promising method to cure disorders and diseases of the central nervous system. In addition to NSCs, other types of stem cells including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem/stromal cells (MSCs) are considered options for transplantation. However, it is worth noting that although numerous animal experiments have been implemented and results reflecting a certain amount of success have been achieved, *in vivo* progress for human subjects in clinical and preclinical trials is still limited. In this review, different types of stem cells used for transplantation therapy of neurological disorders and diseases will be described and an overview presented of advances in stem cell transplantation therapy.

Stem Cells as a Therapeutic Platform

NSCs

In the postnatal mammalian brain, NSC populations are detected mainly in two regions, the SVZ and the SGZ of the hippocampal dentate gyrus (Yang et al., 2017). These cells can be identified by their expression of NSC markers such as Nestin, Musashi-1, CD133, and glial fibrillary acidic protein (GFAP) (Lendahl et al., 1990; Sakakibara et al., 1996; Doetsch et al., 1999; Uchida et al., 2000). The SVZ, a thin layer of dividing cells persisting along the lateral wall of the lateral ventricle, is composed of four cell types: neurogenic astrocytes (type B cells), immature precursors (type C cells), migrating neuroblasts (type A cells), and ependymal cells. SVZ astrocytes (type B cells) remain labeled with the NSC marker SOX2 throughout their long survival in the adult brain, where they divide to give rise to type C cells and then

type A cells, suggesting that SVZ astrocytes act as adult NSCs in both normal and regenerating brain (Doetsch et al., 1999). Ependymal cells, which separate the SVZ from the lateral ventricles, play a significant role in maintenance of the neurogenic niche by inducing neurogenesis and suppressing gliogenesis through secretion of neural regulatory factors, such as the bone morphogenetic protein inhibitor Noggin (Chmielnicki et al., 2004).

In the SGZ of the hippocampal dentate gyrus, NSCs continue to proliferate and differentiate into granule cells that migrate into the granule cell layer of the dentate gyrus throughout life (Gould, 2007). The proliferation rate of NSCs in the SGZ is associated with the age of the animal. In C57BL/6J mice, the rate of neurogenesis in the dentate gyrus is highest during the first month of life, and subsequently declines by 80% when mice are 4 months of age (Ben Abdallah et al., 2010). Evidence has suggested that a few genes important for NSC proliferation, such as Stat3, manifest increased expression in the aging dentate gyrus, while genes modulating neuronal differentiation, such as Heyl, exhibit decreased expression (Shetty et al., 2013).

Self-renewing NSCs isolated from the SVZ and SGZ of adult human brain can generate neurons, astrocytes, and oligodendrocytes *in vitro* (Johansson et al., 1999). Moreover, derived neurons can be supported for prolonged culture with epidermal growth factor (Ayuso-Sacido et al., 2010), fibroblast growth factor-2, and brain-derived neurotrophic factor (Pincus et al., 1998). In summary, *in vitro*-cultured NSCs maintain the capacity for self-renewal, while they can differentiate into various kinds of neurons and glia. These properties provide the foundation of NSC-based therapies.

In the spinal cord, which is typically considered a part of the central nervous system, cells surrounding the central canal in adults acquire stem cell properties in response to injury. Ependymal cells are ciliated cells that line the central canal of the spinal cord. Several NSC markers, such as Sox2, CD133, and GFAP (Hamilton et al., 2009; Fiorelli et al., 2013), have been detected in ependymal cells. After injury, increases in nestin-positive ependymal cells indicate the multipotent properties of ependymal cells (Mothe and Tator, 2005). In response to injury, ependymal cells proliferate and migrate from the periventricular region into the injured area where they differentiate primarily into astrocytes (Mothe and Tator, 2005). Those ependymal-cell-derived astrocytes localize to the center of glia scars, which are considered to have protective effects against neuronal degeneration and the expansion of damage (Kawano et al., 2012).

ESCs

Human ESCs, undifferentiated pluripotent cells isolated from the inner cell mass of a blastocyst, are characterized by a group of surface markers including stage-specific embryonic antigen (SSEA)-3, SSEA-4, TRA-1-60, TRA-1-81, and alkaline phosphatase (Thomson et al., 1998). ESCs have the potential to differentiate into cell types of all three germ layers. In addition, a number of transcription factors including OCT3/4, NANOG and SOX2 have been identified in human ESCs (Niwa et al., 2000; Chambers et al., 2003; Chew et al., 2005). These transcription factors have since been used to induce pluripotent cells from fibroblasts and other somatic cells *in vitro*.

The pluripotency of ESCs, which allows them to differentiate into cell types of all three germ layers, has aroused tremendous research interest in the field of neurological disease treatment. The foundations of ESCs as cell source for therapies for neurological disorders are as follows. First, ESCs can differentiate into neurons and glia after transplantation (Arnhold et al., 2000), and exhibit long-term stability that allows them to integrate into local structure (Nasonkin et al., 2009). Second, neural derivatives of ESCs have the ability to secrete neurotrophic factors that provide trophic support in the injured region (Zhang et al., 2006). Third, ESC-derived neurons of appropriate cortical identity can contribute to the reconstruction of damaged cortical circuitry of the same areal identity (Michelsen et al., 2015). Medial ganglionic eminence-like progenitor cells and retinal progenitor cells differentiated from ESCs have been verified to manifest regenerative significance in AD and retinal degenerative disease, respectively (Liu et al., 2013; Qu et al., 2015).

iPSCs

Successful induction of somatic cells into iPSCs represents a milestone in the field of stem cell and regeneration research. Takahashi and Yamanaka (2006) successfully achieved the induction of pluripotent stem cells from mouse embryonic and adult fibroblasts by introducing four factors (Oct3/4, Sox2, c-Myc, and Klf4) under ESC culture conditions. Almost simultaneously, Yu et al. (2007) established another induction method for iPSCs using a combination of Oct4, Sox2, Nanog, and Lin28. iPSCs obtained from both methods are very similar to ESCs with regard to morphology, proliferation, expression of cell-surface markers, and gene expression profiles. ESC marker genes Esg1, Nanog, Gdf3, and Cripto can be detected in these iPSCs (Takahashi and Yamanaka, 2006). Moreover, Takahashi et al. (2007) successfully induced iPSCs from human dermal fibroblasts with the same four factors in Yamanaka's protocol. These iPSCs are able to form tissues of all three germ layers *in vitro* and in teratomas (Takahashi et al., 2007), suggesting prospects for iPSCs in disease modeling and transplantation therapy. Other cell types from developmentally diverse origins such as hepatocytes, circulating T lymphocytes, and keratinocytes (Chun et al., 2010), have also been successfully reprogrammed into iPSCs with varying efficiencies.

Potential utilization of iPSCs covers a broad range of applications, from constructing disease models to patient-specific therapeutic transplantations (Peng et al., 2016). Indeed, availability of iPSCs from patients suffering from a particular neurological disease is already contributing to the development of better disease models. For example, an iPSC-based model of AD, a neurodegenerative disease, has been established (Israel et al., 2012). iPSC derivatives have also been used to investigate the pathogenesis of retinal degenerative diseases (Gamm et al., 2013). In addition, iPSC derivatives have an intriguing role in experimental therapies for neurological disease. Transplantation of human iPSC derivatives has achieved positive effects in some neurological disease models. For example, in spinal cord injury (Tropepe

et al., 2000), intracerebral hemorrhage (Qin et al., 2013), and retina-related diseases like macular degeneration (Du et al., 2011), iPSCs and their derivatives have achieved valid structural and/or functional recovery.

Retinal stem/progenitor cells

The retina, which is considered part of the central nervous system, was first recognized to possess regenerative characteristics in the middle of the 20th century by researchers investigating salamander eyes (Stone, 1950). In adult vertebrates, numerous investigations have been conducted to identify endogenous stem cells in retina. This research revealed at least three types of cells possessing stem-cell-like properties in the retina, including retinal pigment epithelial (RPE) cells, Müller glial cells, and ciliary pigment epithelial cells.

Human RPE cells remain dormant and quiescent after maturation of the retina, but they can be activated in disease states or by culturing endogenous RPE cells *in vitro*. In certain pathogeneses, such as proliferative vitreoretinopathy (Kim and Arroyo, 2002), RPE cells can transform into a proliferative state after local injury. Moreover, retinal pigment epithelial stem cells, a subpopulation of adult human RPE cells, can be activated *in vitro* into self-renewing, proliferative cells that can differentiate into neural or mesenchymal progenies (Salero et al., 2012). Stem cell multipotency is also detected in Müller glial cells, which can differentiate into photoreceptors after artificially induced degeneration of the retina (Lawrence et al., 2007). Located in the ciliary marginal zone, ciliary pigment epithelial cells are found to proliferate clonally *in vitro* to form spheres before differentiating into retinal-specific cells, such as rod photoreceptors and bipolar neurons (Tropepe et al., 2000), although the efficiency of this process is still unsatisfactory in some research (Gualdoni et al., 2010).

Retinal progenitor cells can also be derived from fetal retinas, which comprise a population of progenitors capable of giving rise to all types of retinal cells (Reh, 2006). Investigations have been conducted to verify the therapeutic efficacy of retinal progenitor cell transplantation. Research in rat models has shown that cultured human retinal progenitor cells integrate into the degenerating retina, whereby they preserve the structure of the outer nuclear layer and elicit improved visual acuity (Luo et al., 2014). Prior to grafting, immunocytochemical analysis showed that cultured human retinal progenitor cells widely expressed NSC markers including nestin, Sox2, and vimentin (Klassen et al., 2007). However, other research demonstrated that rod photoreceptors successfully integrated (formed synaptic connections) and improved visual function, only when rod precursors were transplanted and not proliferating retinal progenitor cells (MacLaren et al., 2006). Thus, these findings suggest different applicable ontogenetic stages of donor cells for successful rod photoreceptor transplantation.

Mesenchymal stem cells (MSCs)

MSCs, also known as mesenchymal stromal cells, are a type of pluripotent stem cell extensively located in various tissues of the human body, especially connective tissues. MSCs were first discovered in human bone marrow (Friedenstein et al., 1968), but can also be isolated from peripheral blood, adipose tissue, muscle, skin, placenta, and amniotic fluid (Yen et al., 2005; Choi et al., 2010; Kim et al., 2013). With increasing understanding of MSCs, researchers discovered their capability to differentiate into cell types of all three germ layers (Safford et al., 2002; Seo et al., 2004; Choi et al., 2010). This attracted a wide range of attention to utilize MSCs as a replacement therapeutic source for various diseases. The neurogenic property and immune modulatory effects of MSCs provide a foundation upon which MSCs can be used to treat neurological disorders (Safford et al., 2002; Bernardo and Fibbe, 2013). In fact, autologous bone marrow-derived MSC treatments of neurodegenerative diseases, including PD and AD, have manifested tremendous therapeutic efficacy in both disease models and clinical trials (Venkataramana et al., 2010; Bae et al., 2013).

Stem Cell Therapies for Neurodegenerative Diseases

PD

The pathological hallmark of PD is a gradual loss of nigrostriatal dopaminergic neurons, which often leads to rigidity, slow physical movements (bradykinesia), tremor and postural instability that severely affects patient quality of life. Current treatments for PD primarily include pharmacological therapies, such as orally administered L-3,4-dihydroxyphenylalanine and dopamine receptor agonists, and deep brain stimulation in which electrodes are surgically implanted into the subthalamic nucleus and globus pallidus. These treatments are effective for amelioration of symptoms, but are inefficient for ceasing disease progression (Lane et al., 2008).

The inspiration for regenerative therapy of PD dates back to transplantation trials of human embryonic mesencephalic tissues two decades ago, whereby histopathological and functional improvements were reported in several experiments and open-label trials (Kordower et al., 1995, 1998; Piccini et al., 1999). However, difficulties in standardizing the cell types present in grafted tissues led to a high variability in the degree of symptomatic relief. In addition, it has been reported that PD pathology might propagate from the host to the graft (Li et al., 2008). Furthermore, ethical concerns prevented further transplantation trials using human embryonic tissues. Therefore, stem cells might be an ideal source for regenerative therapies and have been tested through different strategies.

Cellular sources for tested stem cell therapies of PD include ESCs, MSCs, NSCs, and iPSCs. Dopaminergic cells derived from various stem cell sources have been shown to survive in the host and induce behavioral improvement and motor recovery in mammalian models from rodent to monkey (Takagi et al., 2005; Rodriguez-Gomez et al., 2007). Transplanted cells promote functional recovery primarily through two mechanisms. First, transplanted cells have the ability to survive, express tyrosine hydroxylase, and release and reuptake dopamine, therefore potentially replacing the function of lost or damaged neurons. Second, apart from cell replacement and dopamine release, transplanted stem cells might lead to symptomatic relief through neurotrophic and protective effects. A recent report showed that transplanted NSCs can express brain-derived neurotrophic factor, which can restore

depleted dopamine levels and modulate dopaminergic and glutamatergic systems (Goldberg et al., 2015). In addition, NSC transplantation can also exert neuroprotection through regulation of the host niche, for example, by facilitating local astrocytes undergoing de-differentiation and promoting expression of host-derived growth factors (Zuo et al., 2015).

However, before stem cell therapies can be put into clinical utilization, several critical issues must be taken into consideration: (1) suitable inclusion criteria of patients; (2) the source of stem cells and their eligible accreditation; and (3) the risk of stem-cell-associated tumorigenesis. These issues must be appropriately addressed and several clinical trials have rendered rational references. Although there are no established inclusion criteria for patient selection, several trials have introduced criteria to include patients in their procedures. One study included patients with intact higher mental functions, at least two symptomatic features of PD, and good response to L-3,4-dihydroxyphenylalanine (Venkataramana et al., 2010). Another trial selected patients with motor complications despite adequate oral anti-PD therapy (Venkataramana et al., 2012). To address the problem of cellular source, a whole system was recently established to attain completely xeno-free clinical-grade human ESCs in China (Gu et al., 2017), and a clinical trial of ESC-derived neural progenitor transplantation was subsequently initiated in PD patients. Although the therapeutic effects are still indefinable, their work provides valuable criteria for human ESC production and certification, which contribute to international standards for stem cell therapy. Moreover, utilization of iPSCs has made it possible to obtain cells from the patient's own somatic cells, which alleviates the problem of immune rejection (Wernig et al., 2008). Several studies have demonstrated that no tumor formation occurs during the 10–36 months of their trials (Venkataramana et al., 2010, 2012; Yin et al., 2012) and a long-follow up study reported no sign of tumorigenesis up to 18 years after transplantation (Kefalopoulou et al., 2014). However, it should be mentioned that the life expectancy of PD patients is almost normal. Therefore, even a slight risk of tumorigenesis is unfavorable and current available data do not guarantee the absolute avoidance of tumor formation over prolonged periods of time. After receiving transplantation of stem cells and their derivatives, improvements are detected in PD patients during both "on" and "off" periods of the Unified Parkinson's Disease Rating Scale (Venkataramana et al., 2010, 2012; Yin et al., 2012). These patients were reported to manifest symptomatic improvements, such as a reduction in tremors, rigidity, and freezing attacks (Venkataramana et al., 2012; Bernardo and Fibbe, 2013). Positron emission tomography showed increased dopamine release, while magnetic resonance spectroscopy revealed improvement in N-acetylaspartate/creatine ratio (Brazzini et al., 2010; Yin et al., 2012). These may explain the mechanisms underlying symptomatic improvements. Altogether, current results of clinical trials provide an encouraging perspective for clinical use of stem cell therapies for PD.

AD

AD, which is subclassified into familial AD and sporadic AD, is a progressive neurodegenerative disorder with a prevalence of 46.8 million affected individuals worldwide (Prince, 2015). Pathologically symbolized by β-amyloid (Aβ) senile plaques and phosphorylated TAU protein neurofibrillary tangles, AD can elicit memory, cognition and coordination dysfunction in patients. Current treatments for AD mainly focus on pharmaceutical regulation to deplete accumulated Aβ, such as Aβ-degrading enzymes cathepsin B and neprilysin. However, these drugs are dose-dependent and have no effect on disease progression.

Stem cell sources for treating AD in both animal models and clinical trials range from iPSCs and ESCs to NSCs and their derivatives. Large numbers of animal studies have thoroughly illustrated the characteristics of transplanted stem cells and their derivatives in the brain of AD models, thus paving the theoretical way for clinical trials in AD patients. Animal experiments have demonstrated the following. (1) Transplanted stem cells can migrate into the nervous system and integrate into local neural circuits to enhance synaptogenesis and improve synaptic transmission (Bae et al., 2013; Zhang et al., 2014b). (2) Improved neuropathological features can be detected after transplantation, including reduced deposition and upregulated Aβ clearance (Bae et al., 2013; Shin et al., 2014). (3) Stem cell transplantation decreases neuroinflammation *via* suppressed expression of proinflammatory mediators, such as interleukin (IL)-1, IL-6, and tumor necrosis factor-α (Zhang et al., 2015), and provides long-term protective immunomodulatory effects (Kim et al., 2013). (4) Transplanted stem cells are capable of secreting nerve growth factor and exerting neurotrophic influence (Marei et al., 2015), such that tested animals showed apparent or moderate cognitive and memory improvements (Kim et al., 2013; Zhang et al., 2014b, 2015; Marei et al., 2015). Collectively, this evidence provides a solid foundation for advancing stem cell transplantation therapy into clinical trials.

In addition to therapeutic strategies, stem cells provide novel approaches to model AD. Traditional transgenic mouse models can mimic familial AD symptoms, but the pathological feature of neurofibrillary tangles is not reflected (Elder et al., 2010). Since the successful introduction of human iPSCs, they have been used to successfully model AD (Israel et al., 2012), thus ameliorating problems caused by species-specific differences and allowing for the stratification of drug responses in an era of personalized medicine. The first iPSC model for AD was established by Israel et al. (2012), who collected iPSCs from two familial AD patients, two sporadic AD patients, and two non-demented age-matched control subjects. The results demonstrated that iPSC-derived neurons from familial AD and sporadic AD groups exhibited significantly higher levels of Aβ, phospho-Tau, and active glycogen synthase kinase-3β compared with controls. Neurons from familial AD and sporadic AD patients also accumulated in large Rab5-positive early endosomes compared with controls (Israel et al., 2012). In recent studies, iPSC-based AD models have proved to be an effective tool for understanding the underlying genetic basis of AD, in addition to offering a novel platform for drug screening and toxicology studies (Hossini et al., 2015).

Clinical trials of stem-cell-based therapies have been per-

formed or are underway for AD; at present, all are based on allogeneic approaches. In a phase I clinical trial of nine patients conducted by Kim et al. (2015), human umbilical cord blood-derived MSCs were stereotactically injected into bilateral hippocampus and the right precuneus. Importantly, no patients showed serious adverse events during the follow-up period. Thus, this trial provides proof that stereotactic administration of MSCs is feasible and well tolerated, and it paves the way for further efficacy and clinical benefit studies (Kim et al., 2015). In addition, autologous therapeutic approaches for AD might be established based on iPSC techniques. Patient-specific iPSCs could be genetically modified to provide therapeutic benefits after placing them back into patients (Hunsberger et al., 2015).

Age-related macular degeneration (AMD)

Subclassified into non-neovascular AMD (dry form) and neovascular AMD (wet form), AMD is a neurodegenerative disease that affects the RPE and photoreceptor cells. Affected individuals in both non-neovascular AMD and neovascular AMD suffer from progressive dysfunction and death of RPE cells and photoreceptors. However, neovascular AMD can be more sudden and severe because of fluid leakage or bleeding from highly-permeable vascular networks. Currently, there is no curative treatment for patients affected by AMD. Although, vitamin C and E supplementation is recommended for a small proportion of patients (Sin et al., 2013). For neovascular AMD, administration of anti-vascular endothelial growth factor proved to be applicable; however, this therapy is laborious because of tedious monthly injections and the inability to prevent AMD progression (Young et al., 2014). Macular translocation and RPE transplantation surgeries resulted in decreased visual loss and improvement of vision in some patients (Stanga et al., 2002). These results verified that normal RPE can facilitate the survival and function of photoreceptors, which supports the feasibility of using stem cells and their RPE derivatives as transplantation sources to treat AMD.

Numerous studies have investigated the feasibility and efficacy of stem cells and RPE transplantation to treat AMD, and most studies have shown encouraging results. Tsai et al. (2015) found that transplantation of iPSC-derived neural progenitor cells limited disease progression and reduced retinal pathology resulting from the accumulation of undigested photoreceptor outer segments in rat models. Another study confirmed that ESC-derived neural progenitor cells survived in host retinas and protected retinal structure and function in the early stage following transplantation (Qu et al., 2015). Additionally, subretinal transplantation of bone marrow-derived MSCs significantly rescued dystrophic photoreceptors and yielded a thicker outer nuclear layer in the treated group (Tzameret et al., 2014). Apart from direct stem cell transplantation, the transplantation of RPE cells derived from pluripotent stem cells has also demonstrated efficacy in animal models. RPE cells derived from iPSCs reportedly have the protective capacity to significantly attenuate photoreceptor degeneration on postoperative days 14 and 21, and could survive up to at least 12 weeks after transplantation (Sun et al., 2015). Interestingly, ESC-derived RPE in a polarized monolayer seems to have higher efficacy than ESC-derived RPE cells in suspension. Hsiung et al. (2015) found that polarized human ESC-derived RPE monolayers exhibited resistance to oxidative stress-induced cell death and expressed higher levels of anti-apoptotic signaling factors such as p-Akt and Bcl-2. The safety of pluripotent stem-cell-derived RPE transplantation has also been investigated. In a tumorigenicity study, no tumors were observed with grafting of iPSC-derived RPE sheets during 6–12 months of monitoring, suggesting negligible tumorigenic potential of iPSC-derived RPE (Kanemura et al., 2014). Further, long-term data (spanning the life of animals) showed no gross or microscopic evidence of teratoma/tumor formation after subretinal ESC-RPE transplantation (Lu et al., 2009). These results suggest iPSCs and ESCs could serve as potentially safe sources of RPE for efficacious treatment of AMD.

The first report providing a description of human ESC-derived RPE transplanted into human patients was published in 2012. After transplantation surgery, human ESC-derived RPE showed no signs of hyperproliferation, tumorigenicity, ectopic tissue formation, or apparent rejection, and the vision of AMD patients was slightly improved (Schwartz et al., 2012). The safety of human ESC-derived RPE transplantation was further confirmed by a study in four Asian AMD patients, whereby there was no occurrence of adverse proliferation, tumorigenicity, ectopic tissue formation, or other serious safety issues during the 1-year follow-up (Song et al., 2015b). In another open-label phase I/II study using human ESC-derived RPE, increasing subretinal pigmentation patches, improved visual acuity, and ameliorated vision deficits were observed (Schwartz et al., 2015). However, in a pilot clinical trial of autologous bone marrow-derived $CD34^+$ stem cell transplantation, mild progression of geographic atrophy was noted in both the transplanted eye and contralateral eye during 6-month follow-up, indicating that $CD34^+$ stem cells may not be an ideal candidate to treat AMD (Park et al., 2015). Other recent clinical trials involving stem cell transplantation for AMD are shown in **Table 1**.

Stem Cell Therapy for Traumatic Brain Injury (TBI)

Damage to the brain caused by external mechanical force such as rapid acceleration, blast wave, or penetration wound is defined as TBI, which often leads to impairment of cognition, physical, and psychological functions. TBI involves a complex disease process composed of the primary injury, including contusion and hemorrhage resulting from instant external mechanical disruption, and the triggered secondary injury caused by a cascade of metabolic, cellular, and molecular events such as the imbalance of glutamate and gamma-aminobutyric acid, active oxygen and free radical formation, and impairment of the blood-brain barrier (Xiong et al., 2013). As primary injury occurs immediately after exposure to the external trauma, it can only be preventable. However, the prolonged characteristics of second injury provide a window of opportunity for treatment.

Endogenous neurogenesis has been detected and reported during TBI (Zheng et al., 2013; Thomsen et al., 2014; Goodus et al., 2015). In TBI brain specimens, NSC/neural progenitor

Table 1 Selected stem cell trials in AMD

NCT Identifier	Type of trial	Purpose	Intervention	Primary outcome measures	Trial status	Sponsor
NCT01691261	Phase 1	Phase 1 trial of retinal pigment epithelium replacement in subjects with wet age-related macular degeneration in whom there is rapidly progressing vision loss	Biological: PF-05206388	Incidence and severity of adverse events	Suspended	Pfizer (Collaborator: University College, London), UK
NCT01344993	Phase 1/ Phase 2	To evaluate the effect and to perform exploratory evaluation of potential efficacy endpoints of human ESC-derived RPE cells in patients with AMD	Biological: MA09-hRPE	Safety of hESC derived RPE cells	Completed	Astellas Institute for Regenerative Medicine, UK
NCT02749734	Phase 1	To determine the safety and therapeutic effect of sub-retinal transplantation of hESC-RPE in patients with macular degeneration diseases, and explore new treatment modalities for macular degeneration diseases	Subretinal transplantation	Number of participants with Treatment-Related Adverse Events	Recruiting	Southwest Hospital, China
NCT01518127	Phase 1/ Phase 2	To evaluate the behavior of intravitreal injection of of autologous bone marrow stem cells in patients with AMD.	Intravitreal injection of autologous bone marrow stem cells	ETDRS visual acuity change. Primary safety outcome included visual acuity loss of 15 or more ETDRS letters after treatment	Unknown	University of Sao Paulo, Brazil
NCT01632527	Phase 1/ Phase 2	To investigate the safety and preliminary efficacy of unilateral subretinal transplantation of HuCNS-SC cells in subjects with geographic atrophy secondary to AMD	Subretinal transplantation of HuCNS-SC cells	Number of subjects with adverse events. Descriptive analysis of frequency and types of adverse events experienced by each subject during the study period.	Completed	StemCells, Inc. USA
NCT02755428	Phase 0	To assess the efficacy and safety of RPE transplants to treat AMD disease.	To transplant the clinical level human embryonic stem cells derived retinal pigment epitheliums into subretinal space	Number of subjects with adverse events such as the evidence of graft failure or rejection	Recruiting	Chinese Academy of Sciences, China

AMD: Age related macular degeneration; RPE: retinal pigment epithelium; ESC: embryonic stem cell; ETDRS: early treatment diabetic retinopathy study; HuCNS-SC: human central nervous system stem cell.

cell markers, including DCX, Sox2 and NeuroD, were increased in the perilesional cortex (Zheng et al., 2013). In addition, NSCs along the SVZ reportedly undergo robust proliferation with increased regenerative capacity (Thomsen et al., 2014; Goodus et al., 2015). However, this endogenous regenerative neurogenesis is not enough to prevent and restore the damage. In addition, the heterogeneity of TBI pathophysiology makes it difficult to find a sufficiently effective therapy. In consideration of these facts, stem cell transplantations have been tested in both animal models and clinical trials of TBI, and have exhibited promising therapeutic benefits.

A number of pre-clinical studies have verified the significant ameliorative effects of motor, memory, and cognitive impairment elicited by stem cell transplantation in TBI animal models (Bedi et al., 2013; Wang et al., 2013a; Tajiri et al., 2014b). This research provides insight into potential underlying mechanisms. First, transplanted cells exert anti-inflammatory and immunomodulatory properties against the adverse immune response after TBI (Zhang et al., 2013). Indeed, MSC transplantation after TBI was associated with a lower density of activated microglia/macrophages and peripheral infiltrating leukocytes at the injury site (Bedi et al., 2013; Zhang et al., 2013), which led to improved spatial learning. Second, stem cell transplantation contributes to the reduction of neuron/tissue loss and is capable of increasing white matter integrity (Wang et al., 2013a). Upon engraftment of iPSC-derived NSCs into adult rats after spinal cord injury, these cells differentiated and extended axons into the injured spinal cord, frequently penetrating gray matter and forming synapses with other neurons, which functionally restored neural cells and tissues (Cawsey et al., 2015). Third, transplanted MSCs can inhibit vascular permeability and stabilize the structure and function of the blood-brain barrier by modulating vascular endothelial cadherin/beta-catenin signaling (Pati et al., 2011). In addition, Torrente et al. (2014) reported that paracrine factors of human MSCs promoted wound healing and reduced reactive oxygen species production in TBI models, which was beneficial for harnessing disease progression and damage recovery.

As mentioned above, endogenous neurogenesis is not enough to repair the tissue impairment caused by TBI. However, Tajiri et al. (2013) reported that transplanted human MSCs have the ability to recruit host cells and facilitate endogenous neurogenesis and restoration through a stem-cell-paved "biobridge". After transplantation, a biobridge was established between the neurogenic SVZ and injured cortex. While initially composed of transplanted stem cells, it eventually became overgrown by newly formed host cells. The transplanted cells manifested themselves as pathways for trafficking the migration of host neurogenic cells, but once this biobridge was formed between the neurogenic site and the injured brain site, the grafted cells disappeared and relinquished their task to host neurogenic cells (Tajiri et al., 2013, 2014a). This novel observation linked transplanted human MSCs with endogenous neurogenesis and partially revealed the mechanisms of stem-cell-based therapeutic effects for TBI.

The first clinical trial of 97 TBI patients in whom MSCs were transplanted into the subarachnoid was published in

2013. The results suggested that bone marrow-derived MSCs were safe and effective in TBI patients. Twenty-seven of the 73 patients with motor disorder showed motor function improvements (Tian et al., 2013). In another trial where visual function of patients was impaired as a result of severe cortical injury, the treatment group received intracerebroventricular transplantation of human NSC/neural progenitor cells and exhibited visual function improvement (Luan et al., 2013). In another completed clinical trial, improvement of neurological functions was detected in the group who underwent four umbilical cord-derived MSC transplantations *via* lumbar puncture, including enhanced upper and lower extremity motor functions, sensation, balance, self-care, and social cognition (Wang et al., 2013b). However, there are also clinical trials in which patients suffered from severe adverse effects. For example, a case of acute promyelocytic leukemia in a 36-year-old patient who accepted MSC transplantation treatment for TBI was reported (Song et al., 2015a).

Stem Cell Therapy for Glioblastoma

With a median survival expectation of approximately 12–16 months, glioblastoma is a common form of primary brain tumors that is highly malignant and fatal. Importantly, as glioblastoma has an aggressive nature involving infiltration and invasion, surgical resection is frequently unable to remove all of the glioblastoma foci. This is supported by the fact that most patients die within a year from a reoccurring secondary tumor foci near the resected area (Hochberg and Pruitt, 1980). Further complicating matters, the deep location of tumors and existence of the blood-brain barrier make it sophisticated and difficult for chemical agents to achieve satisfactory therapeutic effects (Sweet et al., 2012).

Since Aboody et al. (2000) first reported the tumor tropism characteristics of NSCs, utilizing NSCs engineered with cytotoxic agents to "home" to glioblastoma has been studied as a potential therapy. Various NSC lines have been investigated for their tumor-tropic migration, including human HB1.F3 NSCs (Zhao et al., 2008), iPSC-derived NSCs (Yamazoe et al., 2015), bone-marrow-derived MSCs (Hu et al., 2012), and adipose tissue-derived MSCs (Liu et al., 2014). Although numerous studies have been conducted to examine the mechanism underlying the tumor tropism of stem cells, it remains incompletely understood. It seems that hypoxia present within the glioblastoma contributes to tumor tropism. During hypoxia, glioblastoma cells upregulate the expression of several chemoattractants and pro-angiogenic factors, such as hypoxia-inducible factor-1 alpha and its downstream targets stromal-cell-derived factor-1 and vascular endothelial growth factor, that attract stem cells to migrate towards the tumor foci (Zhao et al., 2008; Zhang et al., 2012). One study demonstrated that glioma stem cells, a small neural stem-like population of tumor cells, exhibited enhanced chemotaxis for NSC tropism compared with other more differentiated cells. Chemokines expressed by glioma stem cells, such as vascular endothelial growth factor, epidermal growth factor, and basic fibroblast growth factor, contributed to the hypoxia-enhanced NSC-tropic migration (Zhang et al., 2014a). This study suggested a crucial role of glioma stem cells in the migration of NSCs.

A variety of anti-glioblastoma substances have been integrated into NSCs as cargos to kill tumor cells, including cytokines, enzyme/pro-drugs, and oncolytic viruses. Cytokines of the interleukin families, including IL-4, IL-7, and IL-23, manifested antitumor efficacy that could be explained by interleukin-mediated increased infiltration of anti-tumor immune cells and an enhanced immune response (Benedetti et al., 2000; Yuan et al., 2006; Gunnarsson et al., 2010). Tumor necrosis factor-related apoptosis-inducing ligand, a cytokine that can activate caspase-8-dependent apoptosis, dramatically inhibited tumor growth (Kauer et al., 2012). In addition, stem cells carrying enzymes capable of transferring inactive pro-drugs into active and toxic substances is another strategy to treat glioblastoma. For example, herpes simplex virus type 1 thymidine kinase (HSV-tk) phosphorylates ganciclovir (GCV), such that the latter incorporates into DNA to disturb DNA synthesis in glioblastoma cells. The HSV-tk/GCV system has been tested in preclinical studies and the results showed increased tumor cell death and repressed tumor growth (de Melo et al., 2015). Another pro-drug activating enzyme is cytosine deaminase, which transfers 5-fluorocytosine to toxic 5-fluorouracil to cause glioblastoma cell death. Indeed, significant tumor volume reduction was detected in model animals who received transplantation of cytosine deaminase-expressing NSCs and MSCs (Jung et al., 2015). The oncolytic virus strategy involves viruses with the ability to infect, replicate within, and then lyse glioblastoma cells. NSCs loaded with replicating oncolytic adenovirus distribute prominently around tumor margins (Morshed et al., 2015) and can infect glioblastoma cells. Moreover, studies using stem cells loaded with myxoma virus and herpes simplex virus have demonstrated efficacy for repressing tumor growth (Josiah et al., 2010; Duebgen et al., 2014).

Although a large amount of intriguing and exciting research has explored the feasibility of stem cell therapy for glioblastoma, only a few clinical trials are completed or in progress. In a completed pilot study, genetically modified NSCs were injected at the tumor site after surgical resection of the tumor foci (NCT02039778). Thus, further studies are needed to determine immunogenicity, efficacy, and optimum route of NSC transplantation.

In vivo Tracing of Transplanted Stem Cells in the Brain

The development of techniques to monitor the functional consequences of stem cell grafts after transplantation treatments is highly important. Tracing the fate of stem cells in the brain can be performed by direct labeling or the introduction of reporter genes. Direct labeling is based on imaging agents, such as radiotracers for nuclear imaging, or superparamagnetic iron oxide nanoparticles (Steinbeck and Studer, 2015). Alternatively, stem cells can be genetically modified to express reporter genes. The most commonly used reporter genes are luciferases for bioluminescence imaging and the transferring performed for MRI images (Duffy et al., 2014). Use of tracing techniques will lead to important discoveries about stem cell survival, migration, retention, and therapy monitoring.

Conclusion and Perspective

Over the decades, both basic scientists and clinicians have put tremendous efforts into the translation of stem cell therapies for treatment of neurological disorders. Preclinical research using disease models has yielded a large amount of evidence supporting the feasibility and efficacy of stem cell therapies. Clinical trials are also completed or underway for several neurological diseases, such as PD, AD, and AMD. However, in spite of these impressive and inspiring breakthroughs, major obstacles continue to hinder translation from basic research to real clinical application. These obstacles cannot be overlooked before stem cell therapies enter practical utilization.

Generating the right types of cells and understanding underlying therapeutic mechanisms are both important aims to be considered. For example, substantial improvement in PD requires specific types of dopaminergic substantia nigra neurons. However, the situations in AD and TBI are more complex, as is often the case for neurological diseases, as various categories of cells are involved including neurons, glial cells, and vascular endothelial cells. Thus, transplanted cells may have to differentiate into several cell types to exert therapeutic effects. Cell replacement, whereby stem cells and their derivatives replace impaired or lost cell types to restore function, is considered to be the major mechanism underlying efficacy of stem cell transplantation. However, other mechanisms, such as the secretion of neurotrophic factors, immune modulation, and stimulation of endogenous neurogenesis also reportedly contribute to observed therapeutic effects. Thus, it is inadequate and irresponsible to administer stem cell therapies in patients without thoroughly understanding the underlying mechanisms.

Current models of neurological disorders cannot completely reflect all aspects of a disease, which makes it risky, at least to some degree, to put basic research outcomes into clinical use. First, rodent models are unable to duplicate the exact physiological status of humans. Many models of AD use young, otherwise healthy mice, while the clinical situation for AD patients includes advanced age frequently with other chronic medication. Second, animal models are sometimes insufficient for demonstrating substantial improvement of clinically relevant functional deficits. For example, in PD rodent models, stem cell therapy was reported to attenuate rotational asymmetry. However, this deficit does not reflect any symptom observed in PD patients. Third, some adverse effects of stem cell therapy cannot be fully discovered by animal model studies. When dyskinesia was detected in patients who received human embryonic dopamine-neuron transplantation, it came as a surprise, because no preclinical studies had observed such adverse effects (Freed et al., 2001).

Another obstacle is about tumorigenicity and adverse effects. Patients of some types of neurological disorders, PD patients for example, have a virtually normal life expectancy. In that case, even a minor possibility of tumor formation associated with stem cell therapy would be intolerable. Thus, more efforts should be made to thoroughly understand the mechanism of tumorigenicity of stem cells and their derivatives. In some clinical trials, devastatingly severe adverse events are detected, either related to the surgery or effects triggered by the stem cells. In a patient with TBI, acute promyelocytic leukemia occurred after autologous bone marrow-derived MSC transplantation, and the patient later died of disseminated intravascular coagulation. Basic researchers and clinicians are supposed to work together to minimize the possibility of such serious events and related damage to patients.

To enter clinical application, a stem cell therapy needs to hold sufficient competitiveness compared with other conventional therapies, both in availability and therapeutic effectiveness. Currently, the sources of stem cell therapy, including ESCs and NSCs from human embryos or iPSCs from patients, are limited and associated with several problems, which may greatly increase the financial cost of stem cell therapy. ESC therapy is associated with ethical concerns and graft rejection. Meanwhile, the induction rate of iPSCs from patient somatic cells is relatively low, and may increase the cost of personalized treatment (Gamm et al., 2013). In the future, technical and protocol improvements are in great need to maximize the therapeutic effects and minimize the financial costs of stem cell therapies; only then will they finally be clinically competitive and useful.

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