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Review

Clinical results of neurorestorative cell therapies and therapeutic indications according to cellular bio-proprieties

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ABSTRACT

Cell therapies have been explored to treat patients with nervous diseases for over 20 years. Even though most kinds of cell therapies demonstrated neurorestorative effects in non-randomized clinical trials; the effects of the majority type cells could not be confirmed by randomized controlled trials. In this review, clinical therapeutic results of neurorestorative cell therapies according to cellular bio-proprieties or cellular functions were introduced. Currently it was demonstrated from analysis of this review that some indications of cell therapies were not appropriate, they might be reasons why their neurorestorative effects could not be proved by multicenter, randomized, double blind, placebo-controlled clinical trials. Theoretically if one kind of cell therapy has neurorestorative effects according to its cellular bio-proprieties, it should have appropriate indications. The cell therapies with special bio-properties is promising if the indication selections are appropriate, such as olfactory ensheathing cells for chronic ischemic stroke, and their neurorestorative effects can be confirmed by higher level clinical trials of evidence-based medicine.

Contents

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1. Introduction

Cell therapies have been explored to treat patients with nervous diseases for over 20 years. At the beginning of cell therapy in patients with nervous diseases, both physicians and patients expected these cell therapies would soon cure most incurable nervous diseases, such as Alzheimer's disease (AD), stroke, spinal cord injury (SCI), etc. Varying nervous system diseases were tested to treat through using different kinds of cells no matter what their cellular bio-properties were. Even though many kinds of cells demonstrated neurorestorative effects in non-randomized clinical trials; the effects of many cell types could not be confirmed by randomized controlled trials (RCTs) [1–3]. Until now, most expectations of both physicians and patients have not matendized [1–3]. A few of kinds of cell therapies of RCTs such as olfactory ensheathing cells, demonstrated neurorestorative effects in patients with ischemic stroke or neurodegenerative diseases, and improved patients' quality of life, but not a cure [4]. According to neurorestorative mechanisms including neuroprotection, neurostimulation/neuromodulation, neuroplasticity, neurogenesis, neuroregeneration or axonal regeneration or sprouting, neuroreplacement, loop reconstruction, remyelination, immunomodulation or anti-inflammation, angiogenesis or revascularization, and others, each kind of cell plays a neurorestorative role through one or several neurorestorative mechanisms for being transplantation [5,6]. After understanding the functions and bio-property of each kind of cell and knowing what they can do, one could reasonably expect how they could restore dysfunctions for incurable nervous diseases. Cell therapies can not solve all neurorestoring issues in one day or all neurological diseases. In this review, we introduce clinical results of the main kinds of cells their indications and the prospect in the clinic according to their functions and bio-properties.

2. Classification and clinical therapeutic results of the main kinds of cells according to cellular functions or bio-proprieties

According to cellular functions or bio-proprieties, we classified cells into four kinds of cells which have been clinically applied to treat patients with nervous diseases: neurons, neural supportive cells or glias, mixture neural cells and non-neural supporting cells.

2.1. Neurons

2.1.1. LBS neurons

Kondziolka et al. transplanted human neuronal cells ("LBS neurons" originating from teratocarcinoma developed by Layton BioScience, Inc.) in patients with chronic stroke in 2000. Patients showed functional improvements after cell transplantation [7]. However, in a randomized, observer-blinded trial, patients receiving these cells did not show evidence of a significant benefit in motor function [8].

2.1.2. Olfactory neurons

Olfactory neurons (ONs) are cultured from olfactory neuroepithelium. Wang et al. transplanted olfactory neurons (ONs) in a patient with vascular dementia (VD), who improved damaged neurological and psychological behavior by assessing Mini-Mental Status Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) [9]. Guo et al. transplanted ONs in a patient with Alzheimer's disease (AD). The patient showed similar improvements as the VD patient did [10].

2.1.3. Dopamine neurons

Dopamine neurons can be isolated or cultured from embryonic mesencephalic tissue or fetal nigra (ventral mesencephalic tissue) or differentiated from embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), adult CNS, and direct reprogramming of non-neural cells. Freed et al. transplanted embryonic dopamine neurons for patients with severe Parkinson's disease (PD). The transplantation group and the sham-surgery group did not show significant difference of scores on the global rating scale. Interestingly younger but not older patients got some clinical benefits from embryonic dopamine neuron transplantation [11]. Many non-randomized clinical trials of fetal nigral transplantation for patients with PD were reported, and many patients got benefits from the treatment. However, Olanow et al. conducted a double-blind controlled trial of bilateral fetal nigral transplantation in PD patients. Pairwise comparisons were not significant, that is, patients did not get benefits from nigral transplantation [12]. Even worse, following transplantation, off-medication dyskinesia was observed in 13 of 23 patients, but not in any patient in the placebo group [13]. A patient dying 16 years following fetal nigral grafting never experienced clinical benefit, but developed graft-related dyskinesias, even though postmortem analyses demonstrated over 300,000 tyrosine hydroxylase (TH)-positive grafted cells per side [14]. Schweitzer et al. reported transplanted personalized iPSC-derived dopamine progenitor cells into the putamen for a patient with PD, who stabilized or improved at 18–24 months clinical measures of symptoms after implantation [15].

2.2. Glia or neural supportive cells

2.2.1. Olfactory ensheathing cells

Olfactory ensheathing cells (OECs) are cultured from olfactory bulb or neuroepithelium. Huang et al. transplanted OECs in patients

with chronic complete spinal cord injury (SCI) in 2002, who improved their damaged neurological functions and quality of life [16]. These neurorestorative effects of OEC transplantation in chronic complete SCI patients were further confirmed by Rabinovich et al. [17] and more teams [18–25]. However, too many injecting procedures and large injection volume might cause nerve damage and affect the results [26–28]. Many diseases except SCI in the central nervous system (CNS), such as stroke, cerebral palsy (CP), amyotrophic lateral sclerosis (ALS), brain injury, etc. also showed neurorestorative effects following OEC therapy [29–40]. More recently, Wang et al. transplanted OECs in patients with chronic ischemic stroke in a multi-center, randomized, double-blinded, placebo-controlled clinical trial and there were remarkably differences among OEC group, Schwann cells (SCs) group and placebo control group in neurological and daily activity assessments [4].

2.2.2. Schwann cells

SCs are cultured from peripheral nerve. Saberi et al. transplanted autologous SCs in 4 patients with chronic thoracic SCI. Patients did not get benefits from the cell therapy [41]. Intramedullary cell transplantation in 33 patients with chronic SCI was safe during long-term observations [42]. One report of transplanting autologous activated SCs in 6 patients with chronic SCI showed some functional improvements with 5 years of follow-up in a retrospective study [43], but other report of autologous purified SC transplantation in 6 patients with sub-acute complete thoracic SCI did not show clinical improvements [44] and another report of most (7/8) patients with chronic SCI (4 complete and 4 incomplete) did not demonstrated motor and sensory functional improvements [45]. van Horne et al. implanted peripheral nerve grafts into the substantia nigra in patients with PD accompanied with deep brain stimulation, who got benefit with this comprehensive treatment [46]. Quintero et al. conducted a similar procedure as van Horne and got similar results [47].

2.2.3. Oligodendrocytes

Oligodendrocytes are cultured from fetal brain or spinal cord, or differentiated from embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), adult CNS. Progenitor oligodendrocytes differentiated from ESCs was first transplanted to a patient with complete thoracic SCI in a phase I clinical trial in October 2010 [48]. After finishing four cases, this clinical trial was stopped by the Geron company [49,50]. There were no reports about enrolled patients getting benefits from this trial so far.

2.3. Mixture neural cells including special nervous tissue

2.3.1. Mixture neural cells

Mixture neural cells are isolated or cultured from fetal spinal cord or brain, they also can be differentiated from ESCs, iPSCs and mesenchymal stem cells. In some articles they are called neural stem cells. But most of them were identified as progenitor or precursor neurons, astrocytes and oligodendrocytes [51].

Mixture neural cells from fetal spinal cord or brain

Intraspinal transplantation of fetal spinal cord cells for patients with ALS was safe in several clinical studies [52–55] and improved patients' functions in a study [56]. But it did not show differences in the mean rates of progression compared to historical control groups [57]. Transplanting mixture neural cell derived fetal brain in a patient with primary torsion dystonia showed some functional improvement [58]. Transplanting human fetal-derived retinal progenitor cell in patients with retinitis pigmentosa showed significant improvement in the visual acuity [59]. More studies of mixture neural cells from human central nervous system showed safety with or without neurological improvement in patients with nonneovascular age-related macular degeneration [60], neuronal ceroid lipofuscinosis [61], Pelizaeus-Merzbacher disease [62], CP [63], SCI [64].

Levi et al. (2018) reported intramedullary transplantation HuCNS-SC in patients with SCI [65]. Later on, in a single-blind, randomized proof-of-concept study (2019), HuCNS-SC transplantation was found below the required clinical efficacy threshold [66]. Kalladka et al. reported that human neural stem cells (CTX0E03) injected into putamen in patients with chronic ischemic stroke improved neurological function [67]; but in a following study, only a few (4/23) patients with residual upper limb movement at baseline showed improvements in upper limb function [68]; otherwise, patients without residual upper limb movement at baseline did not get any improvements of upper limb movement functions. Zhang et al. transplanted neural stem cell line (NSI-566) into brain in patients with chronic motor deficit stroke and showed some functional improvement [69].

Mixture neural cells from mesenchymal stem cells or hematopoietic stem cells

Transplanting neural stem cell-like cells derived from autologous HSCs into the subarachnoid cavity in patients with CP showed improvements in motor deficit [70]. Intraspinal delivery of bone marrow stem cell-derived neural stem cells in patients with ALS resulted in a temporary stabilization for the first few months post-injection that was gradually deteriorated [71]. Patients with severe traumatic brain injury showed improved neurological functions in different degrees following autologous MSC-derived NSC-like cell transplantation [72].

2.3.2. Retinal pigment epithelium

Retinal pigment epithelium (RPE) are differentiated from ESCs or iPSCs. Several reports showed that patients with age-related macular degeneration [73,74] and Stargardt's macular dystrophy [75], got some benefits from human ESC-RPE implantation. Transplanting a sheet of RPE cells differentiated from induced pluripotent stem cells (iPSCs) in a patient with neovascular age-related macular had not improved or worsened in degeneration visual acuity, and cystoid macular edema was still present [76]. Long-term (four years) observation found that the grafted iPSC-derived RPE sheet survived well, but degeneration visual acuity did not change [77]. Autologous RPE and choroid transplantation for patients with exudative and atrophic maculopathies showed improvement of impaired visual acuity [78]. Autologous retinal transplantation could repair primary and refractory macular holes and patients achieved good anatomic and functional outcomes [79].

2.4. Non-neural supporting cells

2.4.1. Mononuclear cells

Unmanipulated mononuclear cells (MNCs) generally derived from the bone marrow, cord blood, and the peripheral blood.

Syková et al. transplanted the autologous bone marrow MNCs (BMMNCs) in patients with sub-acute and chronic SCI, who improved damaged neurological functions [80].

Additionally, MNCs were used to treat stroke, CP, brain injury, muscular dystrophy patients, Autism, ALS and in brachial plexus injury, etc. Most patients with those diseases got benefits from MNC transplantation in non-randomized, non-double blinded (or observing blinded) and non-sham-controlled clinical studies [1–3], even those benefits were demonstrated in 10 year follow-up [81]. However, Prasad et al. (2014) found that autologous BMMNC therapy in subacute ischemic stroke did not show beneficial effects in a multicenter, randomized trial with blinded outcome assessment [82]. Intravenous infusion of peripheral blood MNCs failed to

show significant differences in neurodevelopment scores between mobilized peripheral blood MNCs and placebo groups after randomization in a randomized, double-blind, cross-over study in children with CP [83]. But the results were a little different in another report about this trial [84]. Some benefits from this trial may be due to intravenous granulocyte colony-stimulating factor. There were no remarkable differences between 7 placebo, and 13 treatment in assessment of GMFM-66 scores during 12 months post-treatment of autologous bone-marrow-derived MNC or autologousumbilical cord blood MNC infusion in a randomized, blinded, placebo-controlled, crossover study [85]. On the contrary, higher cell dosage showed motor function improvements in a randomized, placebo-controlled trial [86]. Human umbilical cord blood-MSC infusion with basic rehabilitation was safe and effective in improving gross motor and comprehensive functions in children with CP [87]. The scores of activities of daily living (ADL), comprehensive function assessment (CFA), and gross motor function measure (GMFM) scales were differences between the human umbilical cord-MSC group and the control group [88]. Intrathecal transplantation of umbilical cord blood MNCs in 36 individuals with spastic CP showed score improvements in modified Ashworth scale (MAS), pediatric evaluation of disability inventory (PEDI), and CP quality of life (CP-QoL) compared to the control [89] (Note: In another article with same registered No. NCT03795974 as this paper, authors called the cells as umbilical cord tissue mesenchymal stem cells [90]). Concomitant administration of allogeneic umbilical cord blood (UCB) infusion and erythropoietin (EPO) showed therapeutic efficacy in children with cerebral palsy (CP) [91]. Subcutaneous granulocyte-colony stimulating factor (G-CSF) demonstrated functional neurological improvements in chronic incomplete SCI (AIS: B, C, D) and in the subacute phase of SCI with a higher level of evidences [92,93].

2.4.2. Mesenchymal stromal cells

Mesenchymal stromal cells are derived or cultured from marrow, adipose tissue, umbilical cord tissue and other sources.

The International Society for Cellular Therapy (2005) believed that unfractionated populations of “mesenchymal stem cells” with recognized biologic properties did not seem to meet generally accepted criteria for stem cell activity, which rendered the name scientifically inaccurate and potentially mislead to the lay public. Thus, the International Society for Cellular Therapy recommended those cells should be named mesenchymal stromal cells (MSCs) [94], and establish their criteria [95,96]. Only “cells” which are identified by special stem cell markers or differentiated into target cells should be called mesenchymal stem cells.

MSCs have been transplanted through intravascular, subarachnoid or direct injection into the lesion area to treat patients with varying diseases, such as SCI, stroke, diffused axonal injury, neuropathic pain, post-traumatic syringomyelia, AD, MS, multiple system atrophy, hereditary spinocerebellar ataxia, brain injury, autonomic nervous system dysfunctions, etc. in non-randomized, non-double blinded (or observing blinded) and non-sham-controlled clinical studies, most of them showed quality of life improvements [1–3]. However the majority of multi-center, randomized, double blind (or observing blind) and sham-controlled clinical MSC trials in neurodegenerative diseases or stroke showed negative results. There were no improvements in neurological functions in a majority of the patients with SCI in a phase 3 clinical trial [97]. A series of higher level evidence (multi-center, randomized, double blinded and sham-controlled) clinical trials for stroke did not exhibit remarkable differences between the cell therapy group and placebo group [98–104]. Even though some trials improved median infarct volume [103] or improved motor scores in lower extremity [103–105].

Lublin et al. (2014) found that human placenta-derived cell (PDA-001) transplantation was safe and well-tolerated, but the efficacy was uncertain for patients with MS in a randomized, placebo-controlled, multiple-dose study [106]. Petrous et al. reported that fewer patients experienced treatment failure in the intrathecally (IT) or intravenously (IV) with autologous MSC groups compared with those in the sham-treated group in patients with active and progressive MS [107]. Gu et al. conducted a randomized controlled trial of human umbilical cord MSCs in 20 patients (another 19 as control) with CP, significant improvements of daily life activity assessments were observed in the human umbilical cord MSC group compared with the control group [108].

The scores of intracerebral stereotactic implantation of modified bone marrow-derived MSCs (SB623) for chronic traumatic brain injury (TBI) were not statistically significant compared with the control group in the functional scales, which included Disability Rating Scale (DRS), Action Research Arm Test (ARAT), gait velocity (GV), T scores of NeuroQOL upper and lower extremity domains and Global Rating of Perceived Change assessed by patient and clinician, although the treated patients significantly exhibited reduction in motor impairment (FMMS) scale scores [109]. A randomized, double-blind, placebo-controlled trial of MSC secreting neurotrophic factor cells for ALS showed similar slope change of Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) in treated and placebo participants [110].

2.4.3. Hematopoietic stem cells

Hematopoietic stem cells (HSCs) derive from the bone marrow, cord blood, and the peripheral blood. Most reports of HSC treatment in nervous diseases were for patients with MS, and patients got some benefits from the treatment. But so far prospective, multicenter, randomized, double blind, placebo-controlled trials were not carried out to assess the clinical efficacy of HSC transplantation for active MS [1–3]. HSC or CD34 also were used to treat other nervous system diseases or damage, such as Duchenne muscular dystrophy, chronic SCI, stroke and ALS, patients with some diseases could improve the function and their quality of life [1–3].

2.5. Combined cell therapies

There are several combining cell therapies, such as, neural cells with non-neural supporting cells, two non-neural supporting cell combinations (MNCs + MSCs or T cells + muscular progenitor cells), non-neural supporting cell combining with Scaffold, and other combinations for patients with SCI, CP, ALS, stroke, etc. Most patients with those diseases got benefits from combining cell therapies [1–3]. But those neurorestorative effects need further to be proved by multicenter, randomized, double blind, placebo-controlled clinical trials.

3. Indications and the prospect of cell therapies for neurological deficits according to cellular special bio-properties

3.1. Neurons

In most normal conditions except for PD, transplanted neurons need ably to live, migrate to area which needs to complement new neurons, integrate with host neurons, and correctly set up synapse connections, then play a normal role. Up to now, there is a little evidence that neurons from common sources can successfully finish those tasks [111]. In PD, transplanted neurons play a role through neurotransmitters (dopamine), which is released by transplanted dopaminergic neurons. Unfortunately transplanted tissue mainly being dopaminergic neurons contained Lewy bodies and did not

express tyrosine hydroxylase and dopamine transporter after they were transplanted several years [112,113]. Human adult olfactory neurons are special cells which can automatically regenerate. After being transplanted, they seem to migrate where they are needed, and become local functional neurons as they need to be compensated or replaced [114]; so the indications of human olfactory neuron therapy should be neurological diseases in which many neurons are lost or die and neurological functions are impaired, such as dementia, PD, etc. Pilot clinical studies demonstrated that patients with PD and VD got benefits from the human olfactory neuron therapy [9,10]. The prospect of the human olfactory neuron therapy is promising, but needs to be proved by multicenter, randomized, double blind, placebo-controlled clinical trials.

3.2. Glias or neural supportive cells

Generally glias or neural supportive cells should support neurorestoration for neurological damage. Axon regeneration in vivo is blocked at boundaries between Schwann cells and astrocytes [115]; transplanted Schwann cells show little intermingling with host astrocytes and therefore limited migration from transplant sites. This leads to the formation of a sharp border between host astrocytes and Schwann cells, which results in axons stalling at the graft–host interface and failing to exit the graft [116]. So Schwann cells may not be able to strongly support neurorestoration in neurotrauma or diseases of central nervous system. No matter what kinds of diseases or damage, there are enough endogenous oligodendrocytes around injured area. Exogenous oligodendrocytes may not be strong enough to restore damaged neurological functions/structures. OECs display Schwann cell and astrocyte properties, which demonstrated neurorestorative effects in patients with chronic ischemic stroke through a multicenter, randomized, double blind, placebo-controlled clinical trial [4,114]. OECs can migrate well between CNS and peripheral nervous system. Indications of OEC therapy may include majority of central nervous diseases and damage. Although promising, it needs to be confirmed by multicenter, randomized, double blind, placebo-controlled clinical trials.

3.3. Mixture neural cells and special nervous tissue

Generally mixture neural cells contain neurons, astrocytes and oligodendrocytes, which can replace lost neurons and restore damaged neurological functions/structures. RPE is promising for age-related macular degeneration. Until now, neurorestorative effects of both mixture neural cells and RPE are not proved by higher level clinical trials of evidence-based medicine.

3.4. Non-neural supporting cells

All non-neural supporting cells (MNCs, MSCs and HSCs) likely share fundamental mechanisms of action mediating their anti-inflammatory and tissue repair functionalities through the cells themselves and their exosomes [97]. They modulate the immunological status to benefit neuroimmunological disease, such as MS. Combination therapy (cells with (G-CSF) may possibly enhance the neurorestorative effects [117]. The therapeutic results for other neurological diseases such as CP, SCI, etc. are contradictory, that is, some are positive, some are negative. So their indications and the prospect for neurological diseases need further research and to be confirmed by multicenter, randomized, double blind, placebo-controlled clinical trials.

4. Comparing therapeutic results among different bio-propriety cells

In order to easlier understand the therapeutic results and their prospective from different cells, we made this table to compare them (see Table 1).

Table 1
Comparing therapeutic results among different bio-propriety cells with or without RCTs and their prospect indications.

Cell types		Main diseases	RCTs		Bio-proprieties	Prospect indications
			Preformed	Results		
Neurons	LBSNs	Stroke	Yes	Negative	Neuroreplacement	Fail for stroke
	ONs	AD, VD	No	Unavailable	Neuroreplacement	Promise for AD,VD
	DNs	PD	Yes	Negative	Neuroreplacement	Fail for PD
Glia or neural supportive cells	OECs	Stroke	Yes	Positive	Nerve repair & neuromodulation	Suitable for stroke & Neurodegeneration
	SCs	SCI	No	Unavailable	Nerve repair & neuromodulation	Need further study for SCI
	ODCs	SCI	No	Unavailable	Nerve repair & neuromodulation	Need further study for SCI
Mixture neural cells including	MixNCs	SCI, Stroke, CP, ALS, TBI	No	Unavailable	Neuroreplacement & nerve repair	Need further study for SCI, stroke, CP, ALS, TBI
special nervous tissue	RPE	MD	No	Unavailable	Neuroreplacement	Need further study for MD
Non-neural supporting cells	MNCs	Stroke	Yes	Negative	Immunomodulation & tissue repair	Fail for stroke
		CP	Yes	Negative or positive	Immunomodulation & tissue repair	Need stronger proofs for CP
	MSCs	Stroke, TBI, SCI, ALS	Yes	Negative	Immunomodulation & tissue repair	Fail for stroke, TBI, SCI, ALS
		CP	Yes	Positive	Immunomodulation & tissue repair	Possibly suitable for CP
		MS	Yes	Negative or positive	Immunomodulation & tissue repair	Need stronger proofs for MS
	HSCs	MS, SCI, ALS, stroke	No	Unavailable	Immunomodulation & tissue repair	Need further study for MS, SCI, ALS stroke

Abbreviation in Table 1: RCT, randomized controlled trial; LBSN, LBS neuron; ON, olfactory neuron; DN, dopamine neuron; OEC, olfactory ensheathing cell; SC, Schwann cell; ODC, oligodendrocyte; MixNC, mixture neural cell; RPE, retinal pigment epithelium; MNC, mononuclear cell; MSC, mesenchymal stromal cell; HSC, hematopoietic stem cells; AD, Alzheimer's disease; VD, vascular dementia; PD, Parkinson's disease; SCI, spinal cord injury; CP, cerebral palsy; ALS, amyotrophic lateral sclerosis; TBI, traumatic brain injury; MD, macular degeneration; MS, multiple sclerosis.
Note: 1. Olfactory ensheathing cells are the only kind of cells which improve the quality of life for patient with stroke in multicenter, double blinded, randomized, placebo controlled clinical trials of cell therapies.
2. Non-neural supporting cells including MNCs, MSCs and HSCs with exosomes can modulate anti-inflammatory and tissue repair functions that may be fit for immunological diseases and nervous damage with inflammation, such as MS, CP and early stage of SCI or TBI.2.Non-neural supporting cells including MNCs, MSCs and HSCs with exosomes can modulate anti-inflammatory and tissue repair functions that may be fit for immunological diseases and nervous damage with inflammation, such as MS, CP and early stage of SCI or TBI.

5. Summary

Up to now clinical cell therapies being conducted in a lot of studies, the majority of them have been non-randomized, non-blind, and non-controlled studies or trials which showed some benefits for patients with varying neurological diseases. Unfortunately most multicenter, randomized, double blind, placebo-controlled clinical trials of cell therapies have not confirmed these cellular neurorestorative effects. According to cellular special bio-properties, each kind of cell therapy should have its own therapeutic indications. The failure showing neurorestorative effects in higher level research of evidence-based medicine may be due to cells which have weak cellular biological neurorestorative role and properties. Olfactory neurons show special property to ably integrate with host neurons, but their clinical neurorestorative effects in AD, VD and other neurological diseases with neuron loss or impairment need to be confirmed by multicenter, randomized, double blind, placebo-controlled clinical trials. OECs showed neurorestorative effects in patients with chronic ischemic stroke in a randomized controlled trial. However more higher level clinical trials should be done for better therapeutic effects through testing transplanting route, dosage and etc. in different phases. Other neural supporting cells, mixture neural cells and non-neural supporting cells should also be done more multicenter, randomized, double blind, placebo-controlled clinical trials for treatment indications to confirm their clinical neurorestorative effects. As soon as proving cell therapy effects, they should be fast translated into clinical routine therapeutic methods to benefit patients with incurable neurological diseases.

Declaration of competing interest

Hongyun Huang holds the patents on OEC and ON culture methods in Beijing Hongtianji Neuroscience Academy. All other authors report no conflicts of interest in this work.

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