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Review

Cell Therapy From Bench to Bedside Translation in CNS Neurorestoratology Era

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Recent advances in cell biology, neural injury and repair, and the progress towards development of neurorestorative interventions are the basis for increased optimism. Based on the complexity of the processes of demyelination and remyelination, degeneration and regeneration, damage and repair, functional loss and recovery, it would be expected that effective therapeutic approaches will require a combination of strategies encompassing neuroplasticity, immunomodulation, neuroprotection, neurorepair, neuroreplacement, and neuromodulation. Cell-based restorative treatment has become a new trend, and increasing data worldwide have strongly proven that it has a pivotal therapeutic value in CNS disease. Moreover, functional neurorestoration has been achieved to a certain extent in the CNS clinically. Up to now, the cells successfully used in preclinical experiments and/or clinical trial/treatment include fetal/embryonic brain and spinal cord tissue, stem cells (embryonic stem cells, neural stem/progenitor cells, hematopoietic stem cells, adipose-derived adult stem/precursor cells, skin-derived precursor, induced pluripotent stem cells), glial cells (Schwann cells, oligodendrocyte, olfactory ensheathing cells, astrocytes, microglia, tanycytes), neuronal cells (various phenotypic neurons and Purkinje cells), mesenchymal stromal cells originating from bone marrow, umbilical cord, and umbilical cord blood, epithelial cells derived from the layer of retina and amnion, menstrual blood-derived stem cells, Sertoli cells, and active macrophages, etc. Proof-of-concept indicates that we have now entered a new era in neurorestoratology.

Key words: Cell therapy; Translational medicine; Neurorestoratology; Central nervous system diseases

BRIEF PROFILE OF NEURORESTORATOLOGY

Definition

Neurorestoratology, a distinct discipline within the neurosciences, has been clearly defined by the International Association of Neurorestoratology as one subdiscipline and one new branch of neuroscience, which studies the therapeutic strategies for neural regeneration, repair, and replacement of damaged components of the nervous system, neuroplasticity, neuroprotection, neuromodulation, angiogenesis, immunomodulation, and their mechanisms to cause improvement. The core of neurorestoratology is to restore neurological function in humans. The research field of neurorestoratology covers various neurorestorative treatments including transplantation of tissue and cells, biomaterials and bioengineering, neuromodulation by electrical and/or magnetic stimulation, pharmaceutical or chemical therapies in neurotrauma, neurodegeneration, cerebrovascular anoxia or ischemia, edema, demyelination, sensory and motor disorders, and neuropathic pain, as well as neural damage resulting from toxic, physical, and chemical factors, immune, infectious, inflammatory, hereditary, congenital, developmental, and other intractable neural lesions (376).

Inexorable Law of Neuroscientific Innovation

Thousands of years ago (approx 2500 B.C.), spinal cord injuries were described as "crushed vertebra in his neck" as well as symptoms of neurological deterioration without treatment in the ancient Egyptian medical papyrus known as the Edwin Smith Surgical Papyrus by the physician and architect of the Sakkara pyramids Imhotep (8). Nearly 90 years ago Ramon y Cajal (1926) stated with certainty: "Once the development was ended, the founts of growth and regeneration of the axons and dendrites dried up irrevocably. In the adult centers, the

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nerve paths are something fixed, ended, and immutable. Everything may die, nothing may be regenerated. It is for the science of the future to change, if possible, this harsh decree" (51). Regeneration and restoration of the central nervous system (CNS) was thought to be almost an impossibility at that time, although scientists still tried to study the special mystery of human life through transplanting brain tissues (374), electrical stimulation (156), nerve growth factor (NGF) administration (204), gene therapy (38), and so forth.

Commonly, physicians of traditional clinical disciplines have believed that sequelae of stroke, CNS trauma, neurodegenerative diseases, and damage lack effective treatments. The majority of the medical community now still think that: "Our knowledge of the pathophysiological processes, both the primary as well as the secondary, has increased tremendously. However, all this knowledge has only led to improved medical care but not to any therapeutic methods to restore, even partially, the neurological function" (8). Unfortunately, the majority of physicians remain ignorant or unaware of the increasing quantity of published evidence concerning CNS functional restoration by neuromodulation, neuroprotection, axon sprouting, neural circuit reconstruction, neurogenesis, neuroregeneration, neurorepair, and neuroreplacement in animal models and patients (109,285,286,303,351,412).

It is the eternal desire for humans to prolong and improve their quality of life, which, with no doubt, it should be the instinct and responsibility of physicians and neuroscientists to search for effective methods. Obviously, it is inappropriate and overly pessimistic for physicians to always say that there is no way to help patients with the sequelae of diseases and damage to the CNS. Therefore, the new discipline, Neurorestoratology, is bound to arise from neuroscientific innovation, filling in the question-marked frame shown in Figure 1, which aims to create effective therapeutic strategies to benefit patients.

Evolution of Neurorestoratology

Restorative Neurology. Dimitrijevic put forward this term in 1985. It was defined as the branch of the neurological sciences that applied active procedures to improve the functioning of the impaired nervous system through selective structural and functional modification of abnormal neurocontrol according to underlying mechanisms and clinically unrecognized residual functions; its intervention strategies included neurostimulation, neuromodulation, and neuroectomies (83), cell transplants (242), drugs (222), and so on.

Restorative Neurosurgery. This term was put forward by Liberson in 1987 (221). Then restorative neurosurgery, as the frontier of neurosurgery, provided the potential to restore lost function. Intervention strategies include gene therapy, neurotrophic factors, and cell transplantation (195,248,321,377), tissue engineering (402), and neurostimulation (172,369).

Neurorestorative Therapy or Surgery. Intervention strategies include cell-based and pharmacological therapies (423) and electrostimulation (373).

Restorative Neuroscience. Intervention strategies include cell transplantation, stimulation, and medicine (11).

Together, all of the medical terms mentioned above were not considered as distinct disciplines, but instead a branch of neurology, neurosurgery, or a specific kind of therapy. The emergence of the term "neurorestoratology," however, signals the birth of a new discipline, which is equally important in comparison with neurology and neurosurgery (59). The potential mechanisms of action of neurorestoratology techniques are highlighted below.

NEURORESTORATIVE MECHANISMS OF CELL THERAPY

Neuroprotection by Neurotrophins and Immune or Inflammatory Modulation

Bone marrow mesenchymal stem cells (BM-MSCs) have the capacity to modulate immune/inflammatory responses in Alzheimer disease (AD) mice, ameliorating their pathophysiology, and improving the cognitive decline associated with amyloid-β (Aβ) deposits (199). Neural stem/precursor cells (NSPCs) can be used as an immune regulatory tool for autoimmune encephalomyelitis (300). In parallel, olfactory ensheathing cells (OECs) play a role in neuroprotection through the secretion of neurotrophins or growth factors (350). Studies by Chopp and colleagues have proven that transplanting MSCs into the brain leads to secretion of neurotrophins, growth factors and other supportive substances after brain injury (307), which change the microenvironment in the damaged area and continually facilitate endogenous neurorestorative mechanisms by reducing apoptotic cell death (55). Garbuzova-Davis et al. (114) and Zwart et al. (429) reported that an appropriate dose of mononuclear human umbilical cord blood (MNC hUCB) cells may provide a neuroprotective effect for motor and optic neurons through the active involvement of these cells in modulating the host's immune inflammatory system response. Neural protection afforded by adipose-derived stromal cells was found to be mostly attributable to activated caspase-3 and Akt-mediated neuroprotective pathway signaling through paracrine support provided by trophic factor secretion (393).

Neurogenesis and Angiogenesis

In early animal studies using neural stem cell treatments, very few cells become neurons (53) and it was

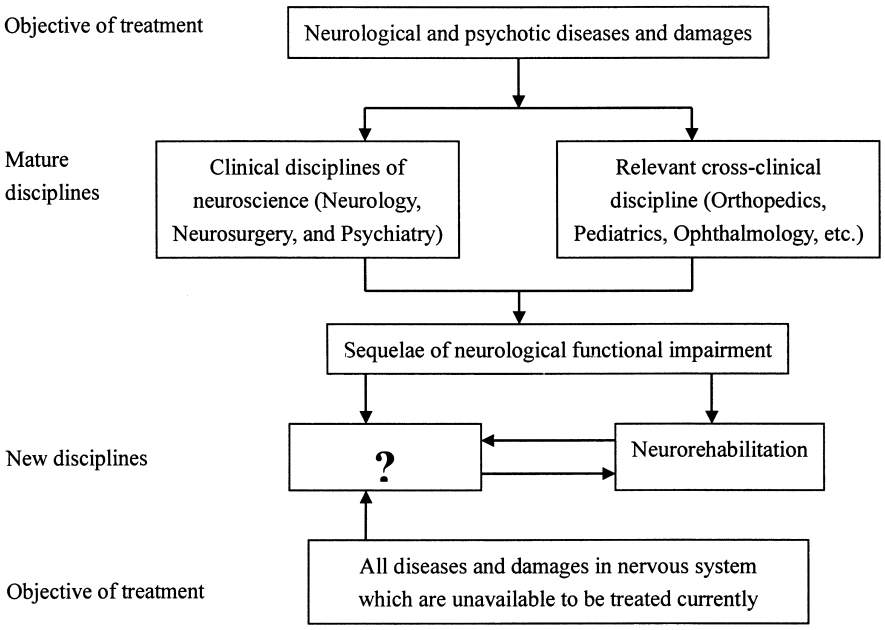

Figure 1. Distribution of disease treated by clinical disciplines of neuroscience and relevant cross-disciplines.

believed that there was no evidence that "new" neurons could reinnervate muscle (256). More studies now indicate that mesenchymal stromal cells (137,206) and neural stem cells could survive, migrate, and differentiate into endothelial cells or glia and neurons (173,427), form electrically active and functionally connected neurons (15) that form synapses between host and donor cells (396), and elicit further functional repair following transplantation into the adult CNS (81,100,161,210,252, 349,382). Furthermore, evidence shows that bone marrow stromal cells are capable of remodeling the blood vasculature (58).

Neurorepair and Remyelination

Many different cell types have been shown to have potential in the repair or remyelination of CNS diseases (28,92,105,261,265).

Neuroregeneration and Sprouting

Schwann cells (SCs) can induce sprouting of motor and sensory axons in the adult rat spinal cord (214). Accumulated studies show that OECs are capable of aiding axon growth or sprouting following transplantation and continued regeneration of the denervated caudal host tract resulting in the recovery of neurological functions in acute (44,211,312,314,409) as well as chronic spinal injury (267).

Neural Circuit or Network Reconstruction, Neuroplasticity, and Neuroreplacement

In the rat stroke model, a graft of medial ganglionic eminence (MGE) cells may differentiate into multiple neuronal subtypes, establish synaptic contact with host cells, increase the expression of synaptic markers, and enhance axonal reorganization in the injured area. Initial patch-clamp recording demonstrated that the MGE cells received postsynaptic currents from the host cells. Functional recovery could be mediated by neurotrophic support, new synaptic circuit elaboration, and enhancement of the stroke-induced neuroplasticity (74). Recent findings of transplanted embryonic dopamine (DA) neurons into the substantia nigra (SN) indicate that DA neurons could extend neurites towards a desired target through the brain stem and caudal diencephalon to reconstruct the neural circuitry from grafted neurons in the host (315,355). Application of stem cells for neuroreplacement therapy is therefore no longer science fiction—it is science fact (367). OECs can promote neuroplasticity in neurodegenerative diseases (62), while NSCs can suppress abnormal mossy fiber sprouting into the inner molecular layer with subsequent reduction of hippocampal excitability (165).

Neuromodulation or Unmasking and Signaling Repair by Micromilieu Change

Our clinical study showed that patients with chronic spinal cord injury have rapid recovery of some functions following OEC transplantation. The explanation is that they changed the local microenvironment by the secretion of useful chemicals or growth factors, which can promote the nerve cell growth, unmasking the quiescent axons, and therefore restoring some of the lost functions (147). Grafting dental pulp stem/stromal cells (DPSC)

can promote proliferation, cell recruitment, and maturation of endogenous stem/progenitor cells by modulating the local microenvironment through enhancing ciliary neurotrophic factor (CNTF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) as stimulators and modulators of the local repair response in the CNS (142) and neuromodulation would likely be necessary to realize the full potential of NSC grafts in restoring function (111). Another study also suggested that the inhibitory neurotransmitters γ-aminobutyric acid (GABA) and glycine secreted by transplanted cells could be an effective clinical tool for treating spinal cord injury (SCI)-associated neuropathic pain (91).

Generally, the patient's functional restoration originated from some or all of the mechanisms as listed above. But under many conditions, functional recovery is from neuromodulation or unmasking, neuroprotection, sprouting, neural circuit reconstruction, and neuroplasticity by neurotrophins, immune or inflammatory modulation and local microenvironment change, and in a few cases from neurogenesis or neuroregeneration, and neurorepair (378,409). Neuroreplacement may be an important tool for Parkinson's disease (PD), but may not be a major way for functional neurorestoration in most other CNS diseases or damage. It remains unclear how to explain the exact mechanisms for clinical functional recovery; in the future mechanisms by which cell transplantation enhances functional recovery need to be better understood following further experimental study.

PRECLINICAL STUDIES OF CELL-BASED NEURORESTORATOLOGY IN CNS DISEASES

Fetal/Embryonic Brain Tissue

In 1977, the first evidence was presented that grafts of fetal brain tissue to the adult CNS could counteract an experimentally induced neurological deficit (279). Cell/tissue suspensions, dissociated from selected embryonic brain regions, can mediate considerable reinnervation of a previously denervated brain or spinal cord region, and they can replace neurons intrinsic to a particular target after intracerebral or intraspinal grafting (277,294). Fetal brain tissue, grafted into the CNS of neonatal and adult animals, has been shown to survive and differentiate (318). In brain tissue grafts consisting of undifferentiated matrix cells and few neuroblasts, good development was observed both in the lateral ventricle and inside the parenchyma, 30 and 110 days after transplant. They differentiated into organotypical and histotypical structures and cells similar to those formed in normal development. Nerve and glial cells of these transplants were well differentiated and tightly connected with the surrounding nervous tissue of the host (7). It has been convincingly shown that grafting of fetal/embryonic brain cells/tissue into the brain and/or spinal cord is a useful alternative therapy for a variety of degenerative and traumatic disorders (Table 1). It has been argued that neural transplantation can promote functional recovery by the replacement of damaged nerve cells, the reestablishment of specific nerve pathways lost as a result of injury, the release of specific neurotransmitters, or the production of factors that promote neuronal growth (260,343,360).

Fetal/Embryonic Spinal Cord Tissue

The first successful transplantation of fetal spinal cord into adult spinal cord was reported in 1983 (291). Some topographical features of the normal spinal cord may be represented in mature spinal cord transplants (318). Embryonic spinal cord transplants are capable of replacing damaged intraspinal neuronal populations and restoring some degree of anatomical continuity between the isolated rostral and caudal stumps of the injured mammalian spinal cord (317). Improved hind limb behavioral deficits were observed after fetal spinal cord homografts (31). Moreover, the grafted fetal/embryonic tissue may stimulate partial regression of an established glial scar (141), replace missing motoneurons (353), and form myelin (324). Data have shown that spinal cord transplants support regrowth of adult host axons resulting in reconstitution of synaptic complexes within the transplant that in many respects resemble normal synapses. Transplants of fetal spinal cord may also contribute to behavioral recovery by rescuing axotomized host neurons that otherwise would have died. Electrophysiological investigations of functional recovery after intraspinal transplantation have been recorded (32,375).

Olfactory Ensheathing/Precursor Cells

OECs are cells that display Schwann cell or astrocyte-like properties. They are a source of growth factors and adhesion molecules that play a very important role as a neuronal support enhancing cellular survival (179, 292). Transplants of these cells have been shown to have a neuroprotective effect, supporting axonal regeneration, remyelination of demyelinated axons, neuroplasticity, neuromodulation, neurogenesis, angiogenesis, anti-inflammatory response, reducing scar and cavity formation, and/or strong phagocytic activity (107,196,203,233,292, 293,311,341,388,397,398,419). The cellular composition of the olfactory tissue and the evidence that equivalent cell types exist in both rodent and human olfactory mucosa suggest that it is potentially a rich source of autologous cells for transplant-mediated repair of the CNS (224). Selected relevant studies are listed in Table 2.

Schwann Cells

Schwann cells (SCs) play a pivotal role in the maintenance and regeneration of the axons in the peripheral

Table 1. Selected Literature in Preclinical Therapeutic Application of Fetal/Embryonic Brain Cells/Tissue

Disease	Animal Host	Year	Reference	Publication Title
Spinal cord trauma				
Hemitransected cord	cat	1992	401	In vivo magnetic resonance imaging of fetal cat neural tissue transplants in the adult cat spinal cord
Transected cord	rat	1977	279	Monoaminergic reinnervation of the transected spinal cord by homologous fetal brain grafts
	rat	1984	68	Fetal locus coeruleus transplanted into the transected spinal cord of the adult rat: Some observations and implications
Visual deficits	rat	1985	361	Fetal brain tissue transplants reduce visual deficits in adult rats with bilateral lesions of the occipital cortex
Peripheral nerve injury				
Sciatic nerve crushed	rat	1983	30	Viability, growth, and maturation of fetal brain and spinal cord in the sciatic nerve of adult rat
Parkinson's disease	rat	1979	294	Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system
Cognitive deficits	rat	1983	193	Fetal brain transplant: Reduction of cognitive deficits in rats with frontal cortex lesions
	rat	1987	29	Fetal brain transplants induce recuperation of taste aversion learning
Brain trauma				
Injured motor/sensory cortex	rat	1988	121	Fetal frontal cortex transplanted to injured motor/sensory cortex of adult rats: Reciprocal connections with host thalamus demonstrated with WGA-HRP
Fimbria-fornix lesions	rat	1994	162	The effects of intrahippocampal raphe and/or septal grafts in rats with fimbria-fornix lesions depend on the origin of the grafted tissue and the behavioural task used
Kainate lesioned cerebellum	rat	1989	13	Organization of host afferents to cerebellar grafts implanted into kainate lesioned cerebellum in adult rats
Hypoxic hypoxia	rat	1984	302	Transplantation of embryonic brain tissue into the brain of adult rats after hypoxic hypoxia
Stroke				
MCAo	rat	1998	140	Neurotrophin-mediated neuroprotection by solid fetal telencephalic graft in middle cerebral artery occlusion: A preventive approach
Transient bilateral common carotid artery occlusion	Mongolian gerbils	2001	23	Transplantation of human fetal brain cells into ischemic lesions of adult gerbil hippocampus

nervous system (PNS) due to their ability to dedifferentiate, migrate, proliferate, express growth-promoting factors, and myelinate-regenerating axons (197). Further, SCs have been shown to form myelin after transplantation into the demyelinated CNS. They can remyelinate spinal cord lesions after experimental demyelination, leading in some cases to functional recovery in rodent and primate models (154). However, SCs do not normally enter the CNS, and migration of SCs transplanted into the CNS white matter is inhibited by astrocytes. As SC migration and myelination is mediated by interactions between sets of extracellular matrix molecules with cell surface preoteins, genetic engineering of SCs to alter aspects of these interactions is a possible way forward. Efforts are, therefore, focused on enhancing their migration and functional integration into the lesioned CNS. In addition, efforts are under way to use these cells as tissue engineer seeds and gene delivery vehicles for an array of molecules with repair potential (33,282). The SCs ability to promote restorative efforts has led to

Table 2. Selected Literature in Preclinical Therapeutic Application of Olfactory Ensheathing/Precursor Cells

Disease	Animal Host	Year	Reference	Publication Title
Spinal cord trauma				
Rhizotomized dorsal roots	rat	1994	313	Regeneration into the spinal cord of transected dorsal root axons is promoted by ensheathing glia transplants
	rat	1999	271	Ensheathing glia transplants promote dorsal root regeneration and spinal reflex restitution after multiple lumbar rhizotomy
Rhizotomized ventral roots	rat	2002	289	Spinal implants of olfactory ensheathing cells promote axon regeneration and bladder activity after bilateral lumbosacral dorsal rhizotomy in the adult rat
Hemitransected cord	rat	1997	211	Repair of adult rat corticospinal tract by transplants of olfactory ensheathing cells
	rat	2004	301	Phrenic rehabilitation and diaphragm recovery after cervical injury and transplantation of olfactory ensheathing cells
Transected dorsal column	pig	2000	153	Xenotransplantation of transgenic pig olfactory ensheathing cells promotes axonal regeneration in rat spinal cord
	rat	2003	175	Functional repair of the corticospinal tract by delayed transplantation of olfactory ensheathing cells in adult rats
	rat	2006	339	Protection of corticospinal tract neurons after dorsal spinal cord transection and engraftment of olfactory ensheathing cells
Transected cord	rat	1998	314	Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glia transplants
	rat	2000	312	Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia
	rat	2001	238	Transplantation of nasal olfactory tissue promotes partial recovery in paraplegic adult rats
	rat	2002	239	Olfactory ensheathing cells promote locomotor recovery after delayed transplantation into transected spinal cord
Contusion	rat	2001	146	Olfactory ensheathing glias transplant improves axonal regeneration and functional recovery in spinal cord contusion injury
	rat	2003	297	Delayed transplantation of olfactory ensheathing glia promotes sparing/regeneration of supraspinal axons in the contused adult rat spinal cord
Electrolytic lesions	rat	1998	212	Regeneration of adult rat corticospinal axons induced by transplanted olfactory ensheathing cells
Photochemical lesion	rat	2001	384	Effects of ensheathing cells transplanted into photochemically damaged spinal cord
	rat	2004	232	Increased expression of cyclo-oxygenase 2 and vascular endothelial growth factor in lesioned spinal cord by transplanted olfactory ensheathing cells
X-ray irradiation with focal ethidium bromide injections	rat	1996	106	Schwann cell-like myelination following transplantation of an olfactory bulb-ensheathing cell line into areas of demyelination in the adult CNS
	rat	1998	155	Transplanted olfactory ensheathing cells remyelinate and enhance axonal conduction in the demyelinated dorsal columns of the rat spinal cord

Table 2. Continued

Disease	Animal Host	Year	Reference	Publication Title
	rat	2000	24	Identification of a human olfactory ensheathing cell that can effect transplant-mediated remyelination of demyelinated CNS axons
	rat	2004	89	Superparamagnetic iron oxide-labeled Schwann cells and olfactory ensheathing cells can be traced in vivo by magnetic resonance imaging and retain functional properties after transplantation into the CNS
	monkey	2004	310	Remyelination of the nonhuman primate spinal cord by transplantation of H-transferase transgenic adult pig olfactory ensheathing cells
	rat	2006	338	Molecular reconstruction of nodes of Ranvier after remyelination by transplanted olfactory ensheathing cells in the demyelinated spinal cord
Sciatic nerve resection	rat	1999	385	Olfactory bulb ensheathing cells enhance peripheral nerve regeneration
	rat	2005	391	Effect of olfactory ensheathing cells transplantation on protecting spinal cord and neurons after peripheral nerve injury
Facial nerve transaction	rat	2001	127	Transplantation of olfactory ensheathing cells stimulates the collateral sprouting from axotomized adult rat facial motoneurons
	rat	2002	128	Transplantation of olfactory mucosa minimizes axonal branching and promotes the recovery of vibrissae motor performance after facial nerve repair in rats
Optic nerve injury				
Optic nerve resection	rat	2003	215	Transplanted olfactory ensheathing cells promote regeneration of cut adult rat optic nerve axons
Glaucoma	rat	2008	213	Transplanted olfactory ensheathing cells incorporated into the optic nerve head ensheathe retinal ganglion cell axons: Possible relevance to glaucoma
Parkinson's disease				
6-OHDA lesions	rat	2004	1	Olfactory ensheathing cell transplantation restores functional deficits in rat model of Parkinson's disease: A cotransplantation approach with fetal ventral mesencephalic cells
Amyotrophic lateral sclerosis				
mSOD1	mouse	2007	250	Adult olfactory bulb neural precursor cell grafts provide temporary protection from motor neuron degeneration, improve motor function, and extend survival in amyotrophic lateral sclerosis mice
Cognitive dysfunction				
Kainic acid lesions in CA3	rat	2009	359	Long-term functional restoration by neural progenitor cell transplantation in rat model of cognitive dysfunction: Eo-transplantation with olfactory ensheathing cells for neurotrophic factor support
Stroke				
MCAo	rat	2009	350	A long term observation of olfactory ensheathing cells transplantation to repair white matter and functional recovery in a focal ischemia model in rat

an increasing interest in using SC grafts for repair of CNS damage (Table 3).

Oligodendrocyte/Precursor Cells

Remyelination by transplantation of myelin-forming cells is possible in animal models; evidence suggests that both a precursor-type oligodendrocyte as well as an oligodendrocyte that previously formed a myelin sheath is able to remyelinate the CNS (126,386). Oligodendrocytes or precursor cells are much more invasive and have been shown to migrate from the implantation site to the lesion over a distance of several millimeters (72,387). Indeed, a number of studies have demonstrated that transplanted oligodendrocytes survive in the host brain, migrate out of the graft, and synthesize myelin. These cells, therefore, have potential for myelin repair after experimental demyelination and in human diseases, such as multiple sclerosis, though several findings suggest that OECs and SCs might be more effective than oligodendrocytes induced from isolated CNS tissue (87, 103,153).

Astrocytes

Cultured astrocytes have been reported to survive and migrate following transplantation. Studies have indicated that there are differences in the ability of immature and mature astrocytes to facilitate plastic changes in the adult brain. Immature astrocytes can synthesize trophic factors to support neuronal survival, produce a permissive environment for neurite extension, and reduce scar formation. In contrast, mature astrocytes produce a nonpermissive environment for axon growth and increase scar formation. Purified astrocytes were capable of facilitating behavioral recovery from frontal cortex ablation, demyelinating lesions in spinal cord, and kainic acid (KA) lesions of the striatum (10,104,174,240,392). Implanted cultured immature astrocytes can stimulate axonal regeneration after injury of the postcommissural fornix tract in the adult rat brain (406). In addition, behavior alleviation after astrocyte transplantation was shown in rat models of memory deficit induced by alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid lesions, which is independent of cholinergic recovery. The cultured astrocytes may exert their effects over a short time period (less than 2 weeks) around the lesion site. They can alter the microenvironment and as a result less scar tissue was formed followed by less of a barrier to the regrowth of nerve fibers (43). Furthermore, evidence indicates that astrocytes at an immature stage of differentiation are capable of inducing axon growth from the adult optic nerve (354).

Microglia

Microglia are the principal immune cells in the CNS and are characterized by a highly specific morphology and unusual antigenic phenotype. Evidence from postmortem analysis implicates the involvement of microglia in the neurodegenerative process of several neurodegenerative diseases, including AD and PD. Grafting of activated microglia into the lesioned spinal cord may promote hind limb motor function recovery in rats and reduce the size of the liquefaction necrosis area (228, 418).

Monocyte/Macrophage

Monocytes/macrophages play an integral role in the inflammatory process and angiogenesis as well as acting as defense mechanisms by exerting microbiocidal and immunomodulatory activity. The recruited monocytes/macrophages are capable of regulating angiogenesis in ischemic tissue, tumors, and chronic inflammation. In terms of neovascularization followed by tissue regeneration, monocytes/macrophages should be highly attractive for cell-based therapy compared to other cells due to their considerable advantages: nononcogenic, nonteratogenic, multiple secretory functions including proangiogenic and growth factors and their straightforward cell harvesting procedure (348). Increasing the presence of activated macrophage/microglial cells at a SCI site can provide an environment beneficial to the promotion of regeneration of sensory axons, possibly by the release of cytokines and interaction with other nonneuronal cells in the immediate vicinity (117,305).

Purkinje Cells

Purkinje cells have a therapeutic value for the replacement and reconstruction of a defective cerebellar circuitry in heredodegenerative ataxia. Insignificant amelioration of motor skills was found in mice after solid cerebellar tissue transplantation, while the cell suspension application had no effect (344,357,358).

Tanycyte

Tanycytes (TAs) are the specialized ependymal glia in the CNS, which are located mostly in the ventral wall of the third ventricle and median eminence (ME). They closely interact with local cerebrospinal fluid, blood, and neurons. TA is a common component of the brain barrier system, the brain–cerebrospinal fluid (CSF) neurohumoral circuit, and the immune–neuroendocrine network. Recent data indicate that TAs transplanted into the adult rat spinal cord can support the regeneration of lesioned axons and may represent a useful therapeutic tool for CNS diseases (306).

Dopaminergic Neurons

Intracerebral transplantation of dopaminergic (DAergic) neuron/cells is currently performed as a restorative therapy for PD (273). The success of cell therapy in PD

Table 3. Selected Literature in Preclinical Therapeutic Application of Schwann Cells

Disease	Animal Host	Year	Reference	Publication Title
Spinal cord trauma				
Hemitransected cord	mouse	1995	254	Reinnervation of peripheral nerve segments implanted into the hemisected spinal cord estimated by transgenic mice
Transected dorsal column	rat	1994	214	Schwann cells induce sprouting in motor and sensory axons in the adult rat spinal cord
Transected cord	mouse and rat	1981	2	Influences of the glial environment on the elongation of axons after injury: Transplantation studies in adult rodents
	rat	1995	408	Axonal regeneration into Schwann cell-seeded guidance channels grafted into transected adult rat spinal cord
Contusion	cat	1982	403	Reconstruction of the contused cat spinal cord by the delayed nerve graft technique and cultured peripheral non-neuronal cells
	rat	1993	249	Syngeneic grafting of adult rat DRG-derived Schwann cells to the injured spinal cord
Photochemical lesion	rat	1994	46	Transplantation of purified populations of Schwann cells into lesioned adult rat spinal cord
Compression injury	rat	1987	389	Chronic regenerative changes in the spinal cord after cord compression injury in rats
Diphtheria toxin injection	cat	1980	133	Remyelination by cells introduced into a stable demyelinating lesion in the central nervous system
Lysolecithin injection	mouse	1981	88	Transplantation of rat Schwann cells grown in tissue culture into the mouse spinal cord
X-irradiation with ethidium bromide injection	cat	1985	36	The use of cultured autologous Schwann cells to remyelinate areas of persistent demyelination in the central nervous system
	rat	1987	37	Schwann cell remyelination of CNS axons following injection of cultures of CNS cells into areas of persistent demyelination
Optic nerve injury	rat	1995	135	Schwann cells and the regrowth of axons in the mammalian CNS: A review of transplantation studies in the rat visual system
Monocular deprivation	rat	1994	296	Schwann cells transplanted in the lateral ventricles prevent the functional and anatomical effects of monocular deprivation in the rat
Parkinson's disease				
MPTP	mouse	1990	75	Cografts of adrenal medulla with peripheral nerve enhance the survivability of transplanted adrenal chromaffin cells and recovery of the host nigrostriatal dopaminergic system in MPTP-treated young adult mice
	monkey	1994	67	Peripheral nerve-dopamine neuron co-grafts in MPTP-treated monkeys: Augmentation of tyrosine hydroxylase-positive fiber staining and dopamine content in host systems
6-OHDA-induced hemiparkinsonism	monkey	2004	407	Therapeutic study of autologous Schwann cells' bridge graft into the brain of hemiparkinsonian monkey
Brain trauma				
Septal-hippocampal lesions	rat	1985	187	Transplants of Schwann cell cultures promote axonal regeneration in the adult mammalian brain
Unilateral fornix transaction	rat	1996	362	Reconstruction of transected postcommissural fornix in adult rat by Schwann cell suspension grafts
Brain stem injury	rat	2003	390	Schwann cells transplantation promoted and the repair of brain stem injury in rats

greatly relies on the discovery of an abundant source of cells capable of DAergic function in the brain. DAergic neuron/precursor cells derived from human embryonic stem (hES) cells, human-induced pluripotent stem (hiPS) cells, neural stem/progenitor cells, human mesenchymal stem cells, and skin-derived stem cells could be increasingly considered as a pivotal choice for transplant (50, 188,227,269,372). It is likely that cell replacement in future will focus on not only ameliorating symptoms of the disease but also try to slow down the progression of the disease by either neuroprotection or restoration of a favorable microenvironment in the midbrain (319).

GABAergic Neurons

Transplantation of predifferentiated GABAergic neurons significantly induces recovery of sensorimotor function in brain injury (25). A deficiency of GABAergic neurons in the neocortex leads to the dysregulation of cortical neuronal circuits, but this can be overcome by cell transplantation. Ventral neural stem cells transfected with neurogenin 1 (Ngn1) are integrated as GABAergic neurons within a few days of transplantation into the adult mouse neocortex, and the transplantation of committed neuronal progenitor cells has been demonstrated to be an effective method for brain repair (268). In addition, transplants of neuronal cells bioengineered to synthesize GABA may alleviate chronic neuropathic pain (90). Fetal GABAergic neurons transplanted into the SN might be an effective means of permanently blocking seizure generalization in kindling epilepsy and probably also other types of epilepsy (101,234).

Cholinergic Neurons

Transplanted cholinergic neurons may reinnervate the host hippocampus, although this reinnervation appears to be different from that seen in the intact hippocampal formation (9). Intraretrosplenial cortical grafts of cholinergic neurons can become functionally incorporated with the host neural circuitry, and the activity of the implanted cholinergic neurons can be modulated by the host brain (216) and it can rectify spatial memory deficits produced by the loss of intrinsic cholinergic afferents from the medial septal nucleus (217). Reconstruction of the septohippocampal pathways by axons extending from embryonic cholinergic neuroblasts grafted into the neuron-depleted septum has been confirmed in the neonatal rat (198). Intrahippocampal septal grafts are able to reinnervate the hippocampal formation and ameliorate spatial learning and memory deficits, which are associated with anatomical and functional incorporation into the circuitry of the host hippocampal formation. Autotransplantation of peripheral cholinergic neurons into the cerebral cortex displayed amelioration of abnormal behavior in AD (160).

Embryonic Stem Cells

ES cells, in particular, possess a nearly unlimited self-renewal capacity and developmental potential to differentiate into virtually any cell type of an organism. They can efficiently differentiate into neural precursors, which can further generate functional neurons, astrocytes, and oligodendrocytes (102,229,231). These cells also have the beneficial properties of secreting neurotrophic and neural growth factors (272). Along with directed differentiation, other current efforts are aimed at efficient enrichment, avoidance of immune rejection, demonstration of functional integration, genetic modification to regulate neurotransmitter and factor release, and directed axon growth with these cells (125).

Neural Stem/Progenitor Cells

Neural stem/progenitor cells (NSPCs) are present during embryonic development and in certain regions of the adult CNS (264). Mobilizing adult NSCs to promote repair of injured or diseased parts of the CNS is a promising approach (3). NSPCs in the adult CNS are capable of generating new neurons, astrocytes, and oligodendrocytes (381). Intraventricular transplantation of neural spheres attenuated brain inflammation in acute and chronic experimental autoimmune encephalomyelitis (EAE), reduced the clinical severity of disease, and reduced demyelination and axonal pathology. Intravenous (IV) NSPCs injection also inhibited EAE and reduced CNS inflammation and tissue injury (27). A recent study showed that adult NSCs transplanted at sites of injury can differentiate into vascular cells (endothelial cells and vascular smooth muscle cells) for vasculogenesis (152). Transplantation of NSCs or their derivatives into a host brain and the proliferation and differentiation of endogenous stem cells by pharmacological manipulations are promising treatments for many neurodegenerative diseases and brain injuries, such as PD, brain ischemia, and SCI (Table 4).

Bone Marrow Stromal Cells

Bone marrow stromal (also called "stem") cells (BMSCs) can be easily amplified in vitro and their transdifferentiation into neural cells has been claimed in vitro and in vivo (63,82,163,171). The possible mechanisms responsible for the beneficial outcome observed after BMSC transplantation into neurodegenerating tissues include cell replacement, trophic factor delivery, immunomodulation, and anti-inflammatory, neuroprotection, and angiogenesis (171,371,379). Transplantation of BMSCs may have a therapeutic role after SCI (64). Adult BMSCs administered intravenously have been shown to migrate into the brain and improve neurological outcome in rats with traumatic brain injury (236). In parallel, data of intracerebral transplantation suggest that bone marrow

Table 4. Animal Model of CNS Diseases Treated Using Neural Stem/Progenitor Cells

Animal Model	Route of Administration	Reference(s)
Spinal cord injury	parenchyma	200,278
	intrathecal	404
	intravenous	42
Traumatic brain injury	intravenous	134
	intracerebral	194
Stroke	intravenous	201,356
	intracerebral	263,363
	intracarotid	129
Parkinson's disease	intracerebral	4,45,93
Lysosomal storage disorders	intracerebral	176
ALS	into spinal cord	410
	intrathecal	150
Hypoxic-ischemic (HI)	intracerebral	288
Experimental autoimmune encephalomyelitis (EAE)	intravenous and intracerebroventricular	299
	intrathecal	298
Huntington's disease	intracerebral	22,322
	intravenous	202
Spinal muscular atrophy	intrathecal	71

could potentially be used to induce plasticity in ischemic brain. Additionally, cotransplantation of BMSCs with ES cell-derived graft cells may be useful for preventing the development of ES cell-derived tumors (253). Results of this field are summarized in Table 5.

Umbilical Cord Mesenchymal Stromal Cells

Mesenchymal stromal cells (MSCs) have now been isolated from most tissues, including the umbilical cord (UC) and UC blood (UCB; see below). UC and UCB MSCs are more primitive than those isolated from other tissue sources and do not express the major histocompatibility complex (MHC) class II human leukocyte antigen-D-related (HLA-DR) antigens. Studies have shown that UC MSCs are still viable and are not rejected 4 months after transplantation as xenografts, without the need for immune suppression, suggesting that they are a favorable cell source for transplantation (422). UC including arteries (UCA), veins (UCV), and Wharton's jelly (UCWJ) is a convenient, efficient source of MSCs that can be expanded easily in vitro for numerous clinical applications for the treatment of nonhematopoietic diseases, and in studies of tissue regeneration and immunosuppression (119,159). UC MSCs have proven to be efficacious in reducing lesion sizes and enhancing behavioral recovery in animal models of ischemic and traumatic CNS injury. Recent findings also suggest that neurons derived from UC-MSC could alleviate movement disorders in hemiparkinsonian animal models. UC-MSC therefore could be a viable alternative to human ES cells or NSCs for transplantation therapy of CNS trauma and neurodegenerative diseases (235) (Table 6).

Umbilical Cord Blood Cells

UCB is a rich source of stem cells with great proliferative potential, besides the bone marrow and peripheral blood; it has the advantage of being an easily accessible stem cell source and is less immunogenic compared to other sources for stem cells (334). There are at least three kinds of stem cells in UCB: hematopoietic, mesenchymal, and embryonic-like stem cells, which are capable of differentiating across tissue lineage boundaries into neural, cardiac, epithelial, hepatocytic, and dermal tissue both in vitro and in vivo (132,325,383). Increasing evidence suggests that MSCs from UCB are present within a wide range of tissues and its therapeutic potential extends beyond the hematopoietic component (34). The expanding population of NSPCs can be selected from the human cord blood nonhematopoietic (CD34-negative) mononuclear fraction (49). UCB can be a potential source for autologous or allogeneic monocytes/macrophages. UCB monocytes should be considered as a primary candidate owing to their easy isolation, low immune rejection, and multiple characteristic advantages such as their anti-inflammatory properties by virtue of their unique immune and inflammatory immaturity, and their proangiogenic ability (333). The therapeutic potential of UCB cells may be attributed to the

Table 5. Animal Model of CNS Diseases Treated Using Bone Marrow Stromal Cells

Animal Model	Route of Administration	Reference(s)
Spinal cord injury	parenchyma	64
	intrathecal	20,275,342
	intravenous	79
Spinal cord ischemia	intrathecal	415
Traumatic brain injury	intravenous	236
	intracerebral	245
Stroke	intravenous	56
	intracerebral	207,414,425
	intracarotid	208
Parkinson's disease	intracerebral	120,209
Demyelinated spinal cord	parenchyma	5,148,340
	intravenous	157
Lysosomal storage disorders	intracerebral	164
ALS	intravenous	70
	intrathecal	131
Hypoxic-ischemic encephalopathy (HIE)	intraperitoneal	123
	intracerebral	415
Experimental autoimmune encephalomyelitis (EAE)	intravenous	420
Huntington's disease	intravenous	86
Peripheral nerve neuropathies	injected into the dorsal root ganglion	69

inherent ability of stem cell populations to replace damaged tissues. Alternatively, various cell types within the graft may promote neural repair by delivering neural protection and secretion of neurotrophic factors (284, 334). In addition, evidence suggests that delivery of circulating $CD34^+$ human UCB cells can produce functional recovery in an animal stroke model with concurrent angiogenesis and neurogenesis leading to some restoration of cortical tissue (295). UCB cells have been used in preclinical models of brain injury and neurodegenerative diseases, directed to differentiate into neural phenotypes, and have been related to functional recovery after engraftment in CNS lesion models (Table 7).

Hematopoietic Stem Cells

Hematopoietic stem cell transplantation (HSCT) was proposed as a treatment for multiple sclerosis (MS) in 1995 based on favorable results in animal models including EAE (47). Recent studies show that transplantation of HSCs from bone marrow is an effective strategy for SCI after directly transplanting cells into the cord 1 week after injury (185), with a similar potential in comparison with marrow stromal cells (180). An in-

Table 6. Animal Model of CNS Diseases Treated Using Umbilical Cord Mesenchymal Stromal Cells

Animal Model	Route of Administration	Reference(s)
Spinal cord injury	parenchyma	411,421
Intracerebral hemorrhage	intracerebral	220
Middle cerebral artery occlusion	intracerebral	219
Global ischemia	intracerebral	166
Parkinson's disease	intracerebral	110,394

Table 7. Animal Model of CNS Diseases Treated Using Umbilical Cord Blood Cells

Animal Model	Route of Administration	Reference(s)
Spinal cord injury	parenchyma	189,426*
	intravenous	170,337
Brain injury	intravenous	237,270
Stroke	intravenous	39,57,400
	intracerebral	84,352,399
	intraarterial	65
Parkinson's disease	intravenous	95
Alzheimer's disease	intravenous	96,274
Huntington's disease	intravenous	94
Amyotrophic lateral sclerosis	intravenous	97,114,115
	intrathecal	131
Hypoxic-ischemic (HI)	intraperitoneal	258
	intravenous	78,413
Aged brain	intravenous	18
Sanfilippo syndrome type B	intravenous	113

*Cell subset: $CD34^+$

creasing number of studies provide evidence that hematopoietic stem cells, either after stimulation of endogenous stem cell pools or after exogenous hematopoietic stem cell use, improve functional outcome after ischemic brain lesions. Various underlying mechanisms such as transdifferentiation into neural lineages, neuroprotection through trophic support, and cell fusion have been deciphered (130). Furthermore, intracerebral peripheral blood hematopoietic stem cell ($CD34^+$) implantation induces neuroplasticity by enhancing β1 integrin-mediated angiogenesis in chronic cerebral ischemia with significantly increased modulation of neurotrophic factor expression in the ischemic hemisphere (352).

Adipose-Derived Adult Stem/Precursor Cells

Adipose tissue is an abundant, accessible, and replenishable source of adult stem cells that can be isolated from liposuction waste tissue by collagenase digestion and differential centrifugation (118). These adipose-derived adult stem (ADAS) cells, which exhibit characteristics of multipotent adult stem cells, similar to those of MSCs, are multipotent, differentiating along the adipocyte, chondrocyte, myocyte, neuronal, and osteoblast lineages (124). ADAS cells have potential applications for the repair and regeneration of acute and chronically damaged tissues (329). As an alternative stem cell source for CNS therapies, ADAS cells labeled with superparamagnetic iron oxide have been shown using MRI to successfully transplant in vivo in unilateral middle cerebral artery occluded (MCAo) mice (320). The study of Ryu and colleagues indicate that improvement in neurological function by the transplantation of ADAS in dogs with SCI may be partially due to the neural differentiation of the implanted stem cells (326). Furthermore, the transplantation of ADAS can promote the formation of a more robust nerve in rats with a sciatic nerve defect and produce a decrease in muscle atrophy (336).

Skin-Derived Precursors

Skin-derived precursors (SKPs) are a self-renewing, multipotent precursor that are generated during embryogenesis and persist into adulthood in the dermis, share characteristics with embryonic neural crest stem cells, including their ability to differentiate into neural crest-derived cell types such as peripheral neurons, SCs, astrocytes, and endothelium (26,149). After transplantation, the cells yield healthy cells that migrate to the lesion site, and then differentiate mainly into cells expressing glia and neuronal markers (122). Recent evidence indicates that transplantation of SKP-derived SCs represent a viable alternative strategy for repairing the injured spinal cord, with the neuroanatomical neurorestorative findings including good survival within the injured spinal cord, reduced size of the contusion cavity, myelinated endogenous host axons, recruited endogenous SCs into the injured cord, formation of a bridge across the lesion site, increased size of the spared tissue rim, myelinated spared axons within the tissue rim, reduced reactive gliosis, and an environment that was highly conducive to axonal growth (35). In addition, SKPs transplanted into PD model rats sufficiently differentiated into dopamine neuron-like cells, and partially but significantly corrected their behavior. The generated DA neuron-like cells are expected to serve as donor cells for neuronal repair for PD (188). Thus, this cell line has been identified as novel, accessible, and a potentially autologous source for future nervous system repair (35,192).

Retinal Pigment Epithelial Cells

The retinal pigment epithelium consists of a unicellular layer of neuroepithelial cells, retinal pigment epithelial (RPE) cells, which are essential for the maintenance of the normal function of the retina (139). Cultured human RPE cells have the capacity to synthesize neurotrophins, including NGF, brain-derived growth factor (BDNF), glial cell-derived neurotrophic factor (GDNF), and neurotrophin-3 (NT-3) (158,262). Studies have shown that, as an alternative cell source, RPE cells possess DAergic replacement properties with neurotrophic support on primary cultures of rat striatal (enkephalinergic) and mesencephalic (DAergic) neurons, and therefore could exert a positive effect in parkinsonian animals by intrastriatal transplantation (247,257,365,366). RPE cells can be transduced with high efficiency using an adenoviral vector, making them promising vehicles for local delivery of therapeutic proteins for the treatment of neurodegenerative diseases in a combined cell and gene therapeutic approach (14).

Amniotic Epithelial Cells

Human amniotic epithelial cells (AEC) do not express the HLA-A, -B, -C, or -DR antigens on their surface, which suggests no acute rejection in transplantation (6). The human amnion membrane serves as a bridge for axonal regeneration in vitro and in vivo; cells isolated from the amniotic membrane can differentiate into all three germ layers, have low immunogenicity and anti-inflammatory function (76,417). Given their multipotent differentiation ability, capability of synthesizing catecholamines including DA, and neurotrophic and neuroprotection effect, there is accumulating evidence that suggests that AECs have therapeutic potential for multiple CNS disorders, such as PD, mucopolysaccharidosis, SCI, stroke, brain trauma, etc. (Table 8).

Menstrual Blood Cells

Endometrial cells supplied as a form of menstrual blood–tissue mixture can be used for cell-based restor-

Table 8. Selected Literatures in Preclinical Therapeutic Application of Amniotic Epithelial Cells

Disease	Animal Host	Year	Reference	Publication Title
Parkinson's disease	rat	2000	167	Human amniotic epithelial cells produce dopamine and survive after implantation into the striatum of a rat model of Parkinson's disease: A potential source of donor for transplantation therapy
6-OHDA lesion	rat	2003	168	Implantation of human amniotic epithelial cells prevents the degeneration of nigral dopamine neurons in rats with 6-hydroxydopamine lesions
MPTP	mouse	2008	183	Transplantation of human amniotic cells exerts neuroprotection in MPTP-induced Parkinson disease mice
Mucopolysaccharidosis type VII	mouse	2001	186	Engraftment of genetically engineered amniotic epithelial cells corrects lysosomal storage in multiple areas of the brain in mucopolysaccharidosis type VII mice
Brain ischemia	rat	2001	280	Amniotic epithelial cells transform into neuron-like cells in the ischemic brain
	mouse	2007	316	Amniotic fluid derived stem cells ameliorate focal cerebral ischaemia-reperfusion injury induced behavioural deficits in mice
MCAo	rat	2008	230	Human amniotic epithelial cells ameliorate behavioral dysfunction and reduce infarct size in the rat middle cerebral artery occlusion model
Spinal cord trauma				
Transection	monkey	2003	335	Role of human amniotic epithelial cell transplantation in spinal cord injury repair research
	rat	2006	405	Transplantation of human amniotic epithelial cells improves hindlimb function in rats with spinal cord injury
Peripheral nerve injury				
Sciatic nerve defects	rat	2004	85	Bridging rat sciatic nerve defects with the composite nerve-muscle autografts wrapped with human amnion matrix membrane
Brain injury	rat	2006	241	Treatment of traumatic brain injury in rats with transplantation of human amniotic cells

ative therapy in muscular dystrophy (380); subsequent evidence shows that populations of stromal stem cells derived from menstrual blood are multipotent, being able to differentiate into chondrogenic, adipogenic, osteogenic, neurogenic, and cardiogenic cell lineages (290). The cultured menstrual blood express embryonic like-stem cell phenotypic markers [Octamer-4 (Oct4), stage-specific embryonic antigen (SSEA), Nanog], and when grown in appropriate conditioned media, express neuronal phenotypic markers [nestin, microtubule-associated protein 2 (MAP2)] (40). Transplantation of menstrual blood-derived stem cells, either intracerebrally or intravenously and without immunosuppression, significantly reduces behavioral and histological impairments in adult ischemic stroke rats (40).

Sertoli Cells

Transplanted testis-derived Sertoli cells, which create a localized immune "privileged" site, possess a modulatory function on graft rejection and survival and act as a viable graft source for facilitating the use of xenotransplantation for diabetes, PD, Huntington's disease, and other neurodegenerative diseases (41,331,332). In addition to producing immunoprotective factors, Sertoli cells also secrete growth and trophic factors that appear to enhance the posttransplantation viability of isolated cells and, likewise, the postthaw viability of isolated, cryopreserved cells (52). Sertoli cells grafted into adult rat brains ameliorated behavioral deficits and enhanced DAergic neuronal survival and outgrowth (331). Cotrans-

planting of Sertoli cells may be useful as a combination therapy in CNS lesions, a strategy that could enhance the recovery benefits associated with transplantation and decrease the need for, and the risks associated with, long-term systemic immunosuppression (399). Further, recent research has shown that implantation of a Sertoli cell-enriched preparation has a significant neuroprotective benefit to vulnerable motor neurons in a superoxide dismutase 1 (SOD1) transgenic mouse model of amyotrophic lateral sclerosis (ALS) (136).

Induced Pluripotent Stem Cells

Induced pluripotent stem (iPS) cells are derived from somatic cells by ectopic expression of a few transcription factors. iPS cells appear to be able to self-renew indefinitely and to differentiate into all types of cells in the body, and are almost identical to ES cells. The generation of patient-derived pluripotent cells applicable to autologous cell-based therapies has the potential to revolutionize medicine (60). Since the first report from Takahashi and Yamanaka on the reprogramming of mouse fibroblasts into pluripotent stem cells by defined factors in 2006 (370), various new methods have been developed to refine and improve reprogramming technology (281). The current demonstration of DAergic differentiation of human induced pluripotent stem cells (hiPSCs), replacement of segmental losses of interneurons and motorneurons due to gray matter damage and restoration of auditory spiral ganglion neurons suggest a new avenue for highly effective, tumor-free, and immune rejection-free cell therapy for PD, SCI, and hearing disturbance in the near future (151,276,323).

CLINICAL STUDIES OF CELL-BASED NEURORESTORATOLOGY IN CNS DISEASES (TABLE 9)

Adrenal Medullary Tissue, Substantia Nigra, and Dopamine Neurons

Positive findings had initially been observed by Backlund et al. (19) and Lindvall et al. (225) concerning the transplantation of autologous adrenal medullary tissue into the striatum of patients with severe parkinsonism. Subsequently, Hitchcock et al. (138), Lindvall and colleagues (226,395), and Madrazo et al. (244) have separately reported that fetal nigral implants might have provided a modest improvement in motor function and have clinically valuable improvements in most recipients within a period of long-term follow-up after transplantation into the brain of patients with PD. Freed and colleagues randomly assigned patients to receive nerve cell transplants or sham surgery with double-blind follow-up. The result showed that transplanted human embryonic DA neurons survive with clinical benefit in younger, but not in older patients (108). Furthermore, pathologic findings suggest that grafts of fetal mesencephalic DA neurons could survive long term with or without α-synuclein-positive Lewy bodies (184,205,259).

Bachoud-Lévi and coworkers indicated motor and cognitive recovery in patients with Huntington's disease after neural transplantation (17), which continued during long-term follow-up (16). The therapeutic value of human striatal neuroblasts in Huntington's disease was identified by Gallina and colleagues (112).

Human Neural Stem/Progenitor Cells or Neuronal Cells

The clinical regimes of intracranial implant of human neuronal cells in stroke patients have proven safe and feasible, though there is a lack of evidence for a significant benefit in motor function (181,182). Data suggest that cell therapy is a safe method and can be effectively used for stroke (308), acute brain injury (346,347), and cerebral palsy (345). In addition, neurological function has been restored after autologous neural stem cell transplantation in patients with brain trauma (428).

Umbilical Cord Mesenchymal Stem Cells

Therapy of UC-MSCs could stabilize the disease course of refractory progressive MS (218).

Umbilical Cord Blood Mesenchymal Stem Cells

Kang and colleagues report that UCB-MSC transplantation may play a role in the treatment of SCI patients (169).

Olfactory Ensheathing Cell and Olfactory Mucosa Autografts

Early OEC/olfactory mucosa autograft transplants for patients with chronic SCI were reported by Huang et al. in 2003 (143), Rabinovich et al. in 2003 (309), and Lima et al. in 2006 (223), and the results were safe, feasible, and positive. Mackay-Sim and colleagues reported autologous OEC transplantation for three patients with chronic SCI with 3-year follow-up was safe, feasible, and one patient showed sensory improvement (243). The therapeutic value of OEC transplantation has been shown in chronic SCI, ALS, cerebral palsy, stroke, MS, and other neurodegenerative diseases and traumatic brain insults in 1,255 patients (144,145).

Schwann Cells

Data from Arjmand and colleagues suggested that autologous SC transplantation is safe for spinal cord injured patients but had no beneficial effects (327).

Table 9. Selected Recent Articles of Clinical Studies Related to Cell-Based CNS Neurorestoratology

Team/Reference	Country	Publication Year	Case Number	Disease	Results
Fassas et al. (99)	Greece	2002	85	multiple sclerosis	effective
Huang et al. (143)	China	2003	171	spinal cord injury	improvement
Park et al. (287)	Korea	2005	5	spinal cord injury	improvement
Bang et al. (21)	Korea	2005	5	stroke	improvement
Rabinovich et al. (308)	Russia	2005	10	stroke	safe & effective
Saccardi et al. (328)	Italy	2006	180	multiple sclerosis	effective
Syková et al. (368)	Czech	2006	20	spinal cord injury	improvement
Yoon et al. (416)	Korea	2007	35	spinal cord injury	improvement
Portaccio et al. (304)	Italy	2007	2	multiple sclerosis	effective
Saiz et al. (330)	Spain	2008	14	multiple sclerosis	safe & effective
Huang et al. (144)	China	2008	15	amyotrophic lateral sclerosis	safe & effective
Mazzini et al. (255)	Italy	2008	9	amyotrophic lateral sclerosis	safe & effective
Moviglia et al. (266)	Argentina	2009	8	spinal cord injury	improvement
Pal et al. (283)	India	2009	30	spinal cord injury	safe
Burt et al. (48)	US	2009	21	multiple sclerosis	effective
Farge et al. (96)	France	2009	347	multiple sclerosis	effective
Suárez-Monteagudo et al. (364)	Cuba	2009	5	stroke	safe & effective
Cristante et al. (73)	Brazil	2009	39	spinal cord injury	safe & improved SSEPs
Cicchetti et al. (66)	Canada	2009	3	Huntington's disease	effective
Huang et al. (145)	China	2009	1255	spinal cord injury, amyotrophic lateral sclerosis, cerebral palsy, multiple sclerosis, stoke, etc.	improvement & effective

Microglia/Macrophage

Knoller et al. reported that autologous macrophages were safe for complete SCI (178).

Bone Marrow Stromal Cell/Hematopoietic Stem Cell/Mononuclear Phagocyte

Research of Appel et al. indicated that peripheral cells derived from donor hematopoietic stem cells were able to enter the human CNS primarily at sites of motoneuron pathology and engrafted as immunomodulatory cells, but they did not provide benefit in sporadic ALS patients (12). On the contrary, autologous anti-human $CD133^+$ mononuclear cell transplantation in the motor cortex delays ALS progression and improves quality of life (251). Furthermore, many studies showed that this kind of cell therapy was feasible, safe, and effective for ALS (78), stroke (21,364), chronic SCI patients (61,77, 266,287,368), and there was also improvement in the acute and subacute phase of chronic SCI (416). Different routes of cell transplantation such as by direct injection into spinal cord, intravenous and intrathecal injection have proven to be equally effective in SCI (116) and traumatic brain injury (424). Evidence shows that autologous hematopoietic stem cell transplantation cannot be deemed a curative treatment but instead may give rise to prolonged stabilization or change the aggressive course of diseases (330). Similar results were reported by Farge et al. (98), Fassas et al. (99), Portaccio et al. (304), and Saccardi et al. (328) as well as in studies for malignant or severe MS (54,177,246).

Nonmyeloablative autologous haemopoietic stem cell transplantation in patients with relapsing-remitting MS reverses neurological deficits (48). Also autologous peripheral blood stem cell transplantation has promoted obvious neurologic improvement for patients with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes syndrome (190,191).

SUMMARY AND PROSPECTS

When entering the 21st century, numerous centers have globally started clinical trials or experimental treatments to investigate the utilization of cells, such as neurons, OECs, bone marrow-derived cells, NSPCs, SCs, etc., for intractable CNS diseases. Despite their diversity in number, clinical status of subjects, route of cell administration, and criteria to evaluate efficacy, the main conclusion drawn from these clinical studies was that such therapies were safe, feasible, and had some neurological functional improvement or restorative effect that improved the patient's quality of life to a varying extent. These achievements had already answered YES or NO to the question of whether the degeneration and damage in the CNS could be functionally restored.

But from the cellular biology viewpoint, there are

several unanswered questions for cell transplantation: what kind of cells would be the best ideal source, the best therapeutic time window, the most suitable selection for patients and diseases of different kinds, and the optimal route. Consequently, emphasis should be placed on solving these questions and evaluating the efficacy of each particular treatment modality in detail.

On the other hand, from a clinical neurorestoratology viewpoint, the current treatment results are far from an effective cure or the miracle effect, as the majority of people expect; however, therapeutic strategies to retard disease progression for neurodegenerative diseases or to improve some functions from acquired damages seem to be a more realistic clinical aim compared with expecting a cure or complete recovery in the present or near future. Patients, scientists, and doctors should value highly the patients' achievements from effective treatment strategies that are currently still thought by some to not be available.

So far, the pleasurable reality is that landmark advances and the results of preclinical and clinical studies in neurorestoratolgy have been driving our traditional concept from the passive reaction to disease to active attempts to restore the lost functions of the CNS. Now people are more interested in and pay more attention to functional neurorestoration rather than the anatomical structure repair of the CNS.

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