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Clinical application of oligodendrocyte precursor cells for cell-based therapy

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Abstract:

Oligodendrocyte precursor cells (OPCs), which give rise to mature oligodendrocytes (OLs), play important roles in maintaining white matter function. Even during the adulthood period, OPCs comprise roughly 5% of all cells in the forebrain and retain a capability to become myelinated OLs. Recently, OPCs have been proposed as a novel source for cell-based therapy. For the purpose, OPCs can be obtained from embryonic stem cells, induced pluripotent stem cells, and directly converted cells derived from patients. Here, we will provide a brief review of the potential of using OPCs as a cell-based therapy for treating various neurological diseases.

Key words:

Cell transplantation, oligodendrocyte precursor cells, stem cell therapy

Introduction

In 1983, morphologically and physiologically, distinct cells were purified as bipotential oligodendrocyte-type-2 astrocyte progenitor cells (O-2A cells), which were immunoreactive to A2B5 antibody.^[1] Since the cells produced oligodendrocytes (OLs), they were called as oligodendrocyte precursor cells (OPCs). However, the original property of OPCs was not restricted to OLs, and the cells expressed NG2 chondroitin sulfate proteoglycan 4.^[2] Therefore, the O-2A cells are now also referred as NG2 cells or polydendrocytes.^[3] The existence of OPCs in central nervous system (CNS) has been widely recognized by utilizing of their immunoreactivity to NG2 and the alpha receptor of platelet-derived growth factor (PDGF-R α).^[4] OPCs comprise 2%–8% of all cells in the human adult forebrain.^[5,6] Under some conditions, OPCs also produce astrocytes and neurons.^[7] Therefore, OPCs may work as multipotent neuronal stem cells and could be a source for cell-based therapy for neurological diseases. In this mini-review, we will briefly introduce the key properties of OPCs and discuss the therapeutic potential of OPCs as a source for cell transplantation.

Oligodendrocyte Precursor Cell Function in Central Nervous System

OPCs are active in developing CNS, and their roles during the developing stage have been extensively

examined in rodents. In spinal cord, OPCs first appear in ventral neural tube in the embryonic stage day 14.5 (rat) and day 12.5 (mouse). The region includes p3 domain defined by the expression of homeodomain transcriptional factor Nkx2.2 and pMN/OL domain defined by the expression of basic helix-loop-helix transcriptional factor Olig2.^[8-10] OPCs in the ventral neural tube are consisting of about 80% of total OPCs in the whole spinal cord. A few days later, OPC is also generated in the dorsal neural tube, consist of about 10% of OPC in the whole spinal cord.^[11] In forebrain, OPCs appear in the ventral region of ventricular zone, initially in medial ganglionic eminence (GE), and afterward in lateral GE, which are defined by the expression of the transcriptional factor Nkx2.1 and Gsh2, respectively. GE-derived OPC migrates into entire parenchyma of the brain with proliferation. OPCs are perinatally generated in the dorsal region of ventricular zone defined by the expression of Emx1 and coexist with GE-derived OPCs mainly in the neocortex. In postnatal period, OPCs are generated from the subventricular zone and distributed into the neocortex and constitutive a small population. These indicate age- and region-dependent differences in OPC cell cycle, and therefore, OPCs originally possess the heterogeneity in brain development.^[12]

Defined Factors Determines Oligodendrocyte Precursor Cells Lineage

Several specific intrinsic factors have been identified to promote endothelial cells in the

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neural tube to organize the OPC population. In the spinal cord, sonic hedgehog (SHH) promotes the development of Olig2-expressing progenitor cells potential to differentiate into somatic motor neuron cells and OPCs.^[13] Although fibroblast growth factor 2 (FGF2) has a positive regulatory effect on the proliferation of OPCs from rodent neural stem cells (NSCs), it blocks the transition of human pre-OPCs to OPCs by SHH-dependent expression of Olig2 and Nkx2.2, suggesting that intrinsic factors could exert its regulatory effect in different stage between species. Phosphorylation of Olig2 also induces to divergence in differentiation into OPCs.^[14] Further specific cell fate as OPCs has been determined by intrinsic transcriptional factor, Sox10.^[15]

Potent extrinsic factors have been identified which proliferate OPCs such as growth factors, neurotransmitters, signaling molecules, and extracellular matrix molecules. PDGF is one of the most potent and characterized molecules that are mainly secreted from astrocytes and neurons. PDGF-AA is a homodimer of PDGF-A subunit, has a high-affinity with PDGF-R α highly expressed in OPCs.^[4] PDGF-A-deleted mice exhibit depletion of OPCs^[16] and PDGF-A transgenic mice show OPCs proliferation,^[17] indicating that PDGF-R α should be a major regulator of OPCs and the sequential maturation into OLs.

Differentiation into Oligodendrocyte Precursor Cells from Stem Cells

According to identified intrinsic or extrinsic factors, OPCs can be differentiated from stem cells. In 1999, glial precursor cells (GPCs) have been reported to be derived from embryonic stem cells (ESCs) and contribute the myelination of the myelin-deficient rat.^[18] In the study, ESCs were aggregated to embryonic bodies (EBs) and plated in a defined medium with epidermal growth factor (EGF), FGF2, and PDGF-AA. Differentiated cells were immunoreactive to A2B5 and O4 as an OL marker and also glial fibrillary acidic protein as an astrocyte marker. Recent advances using dual and Wnt/ β -catenin inhibitors such as LDN, SB431542, XAV induce to robust neural lineage despite of the requirement for lengthy *in vitro* differentiation periods.^[19,20] ESCs were then differentiated into neural epithelial cells express PAX6, pre-OPCs express Olig2, and NKx2.2, and OPCs express PDGF-R α and SOX10 under purmorphamine, a smoothed agonist of the hedgehog pathway.

Induced pluripotent stem cells (iPSCs) have been available for autologous engraftment of disease-relevant cells by directed differentiation using defined factors.^[21] Czepiel *et al.* differentiated from iPSCs into functional OLs through EBs floating culture. To induce neural precursor cells, EBs were dissociated and cultured using FGF2 and EGF. They differentiated into mature OL using PDGF-AA, T3, and NT3, which were able to form myelin around the axon of cocultured dorsal root ganglion neurons *in vitro* and the demyelinated corpus callosum of cuprizone-fed mice without teratoma formation *in vivo*.^[22] Wang *et al.* formed EBs from iPSCs and used FGF2 for neuroepithelial stage, RA, B27, purmorphamine for pre-OPCs and finally, differentiated into OPCs from iPSCs using T3, NT3, insulin-like growth factor (IGF), PDGF-AA, and purmorphamine.^[23] They furthermore isolated OPCs

from iPSCs by fluorescence-activated cell sorting using A2B5, CD140a/PDGF-R α , and CD9 antibodies. OPCs-transplanted homozygous shiverer rag2-null mice deficient in myelin lived almost two-time longer than control. Recipient callosa were densely myelinated and showed no evidence of tumorigenesis. OPCs readily differentiated into not only OLs but also astrocytes. For directing the maturation of OLs, they withdrew half gliogenic growth factors (PDGF-AA, IGF, and NT-3) and supplemented them with half neurobasal media plus B27 and brain-derived neurotrophic factor (BDNF). The majority of transplanted OPCs was OLs and remained OPCs (80%), and the rest of cells were astrocytes in the corpus callosum without any evidence of tumorigenesis *in vivo*. The myelination efficiency of implanted iPSCs-derived OPCs was as high as tissue-derived CD140a-sorted OPCs.^[24]

OPC can be generated from fibroblasts by direct reprogramming^[25-27] by ectopic expression of defined transcriptional factors. Induced OPC (iOPC) can expand *in vitro* and differentiate into mature OL ensheathing host axons and generating compact myelin.

Efficacy of Transplantation of Oligodendrocyte Precursor Cells in Rodent Demyelinated Disease

Several studies have been demonstrated that OPCs transplantation derived from stem cell could be effective for the rodent neuronal disease such as traumatic injury, radiation-induced demyelination, or congenital hypomyelination [Table 1]. The treatment could be fundamentally targeted based on three following principle benefits: (1) remyelination by exogenous OPCs, (2) Stabilization of the necrotic core cavity by placing proliferating OPCs into the lesion (3) enhancement of endogenous self-repairing mechanism by systematic regulation of immune response and protection by release of neurotrophins secreted from transplanted OPCs. Several studies suggested that remyelination is not always necessary for the survival of demyelinated axons^[36,37] suggesting that the combination of both benefits should be required to maximize the therapeutic potential of OPCs for clinical application.

Spinal cord injury (SCI) is a white matter trauma that causes demyelination, OLs death, and remyelination. The underlying mechanisms such as ischemia, free radical production, and phagocytosis by immunoreactive cells lead to OLs cell death within hours and lasts for weeks after injury. OPCs derived from human ESCs survived, differentiated in the C5 midline contusion injury site of the cervical cord, and improve the motor function of forelimb.^[30] In this study, OPCs histologically spared broad white and gray matter, induced to remyelinate and preserved motor neurons, correlated with movement recovery. Transplanted OPCs derived from human ESCs (hESCs) exhibited enhanced remyelination and promoted improvement locomotor ability only at early time points after thoracic SCI.^[29] In other study, OPCs derived from hESCs transplanted into deep sensorimotor cortex migrated massively along the white matter tract and differentiated into ensheathing OLs,^[28] indicating that OPCs can serve as a competent source of OLs after traumatic brain injury. NSCs derived from human fetal spinal cord, or human ESCs survived, differentiated, and filled cavity lesion in the T3 complete spinal cord transection.^[38] The grafted cells primarily differentiated into neurons (27.5%),

Table 1: Oligodendrocyte precursor cell transplantation in rodent model of disease

Source of OPCs	Animal models	Injection route	References
ESC (human)	Traumatic brain injury (rat)	Into deep motor cortex	[28]
ESC (human)	SCI (rat)	Subcutaneous injection	[29]
ESC (human)	SCI (rat)	Subcutaneous injection	[30]
ESC (human)	Radiation-induced demyelination (rat)	Grafted in forebrain	[20]
ESC (mouse)	SCI (rat)	Into dorsal column	[18]
ESC (mouse)	Periventricular leukomalacia (rat)	Into lateral ventricle	[31]
ESC (mouse)	Globoid cell leukodystrophy (mouse)	Into brain parenchyma	[32]
iPS (human)	Congenital hypomyelination (mouse)	Into corpus callosum	[23]
iPS (mouse)	Cuprizone-induced demyelination (mouse)	Into corpus callosum	[22]
BMSC (rat)	LPC-induced demyelination (rat)	Into corpus callosum	[25]
Extracted OPCs (human)	Demyelination (shiverer mouse)	Into corpus callosum	[33]
Extracted OPCs (human)	LPC-induced demyelination (rat)	Into injury site	[34]
Primary OPCs (rat)	Periventricular leukomalacia (rat)	Into cortex	[35]
Fibroblast (mouse, direct conversion)	SCI (mouse)	Into spinal cord	[27]

OPCs: Oligodendrocyte precursor cells, ESC: Embryonic stem cell, LPC: Lysophosphatidylcholine, iPS: Induced pluripotent stem, BMSC: Bone marrow stromal cell, SCI: Spinal cord injury

OLs (26.6%), and astrocytes (15.9%). Graft-derived axons in host white matter myelinated by host OLs and extended over long distances to connect the neural circuit and improved electrophysiological and functional outcomes. GPCs-derived OPC also contributes to myelination.^[18] These studies suggest that the transplanted OPCs could functionally contribute to remyelinate motor neurons in the SCI site and give the additional protective effects other than remyelination on the remaining neurons.

X-irradiation therapy has been applied to many primary and metastatic cancers in the intracranial lesions while X-irradiation cause cognitive impairment as its side effect pathologically consisting of demyelination and necrosis in the white matter, and the main target of radiation is the large pool of mitotically active OPCs.^[39,40] Although endogenous OPCs are present in the injured white matter region after radiation, they fail to remyelinate the demyelinated axons. The establishment of exogenous OPCs requires the condition where endogenous OPCs were completely depleted, and the presence of inflammation^[40,41] implying the needs of activated immune response eliminates remaining aberrantly functional OPCs. Radiation decreased the number of OPCs accompanied with the decreased expression of myelin basic protein (MBP). When ESC-derived OPCs were grafted into the damaged cortex, they migrate throughout the white matter and remyelinate irradiated brain and ameliorates cognitive function. Moreover, when transplanted into the cerebellum, they improved the motor function.^[20] It is under debate whether the improvement of cognitive and locomotive function by OPCs transplantation could be dependent on remyelination or not. Mouse-derived neural progenitor cells transplanted into irradiated mice increased the axon survival by restoring the remyelinating capacity. While there are no signs of axonal degeneration in the chronic stage of genetically mutated MBP mice.^[36] Therefore, transplanted OPCs could contribute to compensate and repair the demyelinated region by some beneficial actions other than myelin sheath production.

Other adult disease such as metabolic disorders of myelin such as globoid cell leukodystrophy, Krabbe's disease, and

Alexander's disease, and neurodegenerative disease associated with white matter loss and ischemic white matter disease are potential targets of OPC transplantation therapy.^[31,32,42] Transplanted OPC promotes the BDNF and the proliferation of NSC, enhancing the endogenous self-repairing system in the ischemic brain. In regard of neural NSC transplantation, NSC overexpressing sphingomyelinase-induced the reduction in accumulated sphingomyelin in sphingomyelin-deficient Niemann–Pick type A model mice.^[43] Engrafted NSC also ameliorated lipofuscin accumulation in the mouse model of neuronal ceroid lipofuscinosis,^[44] raising the therapeutic possibility of the approach to the white matter-related disease by combined transplantation of the NCS and the OPCs.

Overview of Clinical Application of Oligodendrocyte Precursor Cells Cell-based Study

One of the challenging aspects of the clinical approach using stem cell-derived OPCs/OLs is the requirement for lengthy culture for differentiation into late OPC/OL,^[45] which prevents the injured patient from immediate cell-based therapy using stem cell-derived OPCs/OLs. The previous reports showed that it took almost 3 months to obtain functional OPCs derived from ESCs and almost 4 months from iPSCs. Further, 3 months after transplantation ES-derived OPCs matured into OLs and produced dense and compact myelin *in vivo*. One solution is using dual Smad and Wnt/ β -catenin inhibitors which rapidly induce to neuronal lineage and shorten the differentiation period into OL.^[46] OPCs derived from sources other than stem cell could be another solution for immediate OPC cell therapy following demyelinated neuronal disease. Bone marrow stromal cell-derived OPC mitigated demyelination and augmented remyelination in lysophosphatidylcholine-injected demyelinated rodent brain.^[25] Extracted OPCs from fetal or adult brain are also available, which infiltrated into the forebrain when xenografted to congenitally or chemically demyelinated mouse.^[33,34] However, this method is challenging for clinical application since the postmitotic state impedes the large-scale expansion. Ectopic expression of transcriptional factor Oct4 in fibroblast generates self-renewing and bipotent OPC (iOPC), which is a powerful and promising source for

OPC cell-based therapy. This iOPC is available about 1 month after reprogramming and can proliferate through over thirty times of self-renewals. This method bypasses undifferentiated stem cell state and limits the tumorigenic potential after transplantation.^[47] Transplanted iOPCs enhanced recovery of locomotion in a rodent SCI model.^[27]

Taken together, cell-based OPC therapy may give the following beneficial cellular effects in the injured region: Remyelination, heterogeneous OL/astrocytes cell replacement in the cavity, and the enhancement of functional NSC through secreted neurotrophins. Further investigation of the mechanism of OPC lineage and development of stem cell technology will translate the OPC research into clinical benefits for the patients of demyelinating disorders in near future.

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Conflicts of interest

There are no conflicts of interest.

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