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REVIEW

Regenerative therapy for neuronal diseases with transplantation of somatic stem cells

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Abstract

Pluripotent stem cells, which are capable of differentiating in various species of cells, are hoped to be donor cells in transplantation in regenerative medicine. Embryonic stem (ES) cells and induced pluripotent stem cells have the potential to differentiate in approximately all species of cells. However, the proliferating ability of these cells is high and the cancer formation ability is also recognized. In addition, ethical problems exist in using ES cells. Somatic stem cells with the ability to differentiate in various species of cells have been used as donor cells for neuronal diseases, such as amyotrophic lateral sclerosis, spinal cord injury, Alzheimer disease, cerebral infarction and congenital neuronal diseases. Human mesenchymal stem cells derived from bone marrow, adipose tissue, dermal tissue, umbilical cord blood and placenta are usually used for intractable neuronal diseases as somatic stem cells, while neural progenitor/stem cells and retinal progenitor/stem cells are used for a few congenital neuronal diseases and retinal degenerative disease, respectively. However, non-treated somatic stem cells seldom differentiate to neural cells in recipient neural tissue. Therefore, the contribution to neuronal regeneration using non-treated somatic stem cells has been poor and various differential trials, such as the addition of neurotrophic factors, gene transfer, peptide transfer for neuronal differentiation of somatic stem cells, have been performed. Here, the recent progress of regenerative therapies using various somatic stem cells is described.

Key words: Somatic stem cells; Transplantation; Regenerative therapy; Neuronal disease; Neuronal differentiation

Core tip: Pluripotent stem cells, which are capable of differentiating in various species of cells, are hoped to be donor cells in transplantation in regenerative medicine. Somatic stem cells with the ability to differentiate in various species of cells have been used as donor cells for neuronal diseases, such as spinal cord injury, cerebral infarction, amyotrophic lateral sclerosis, Parkinson's disease and multiple sclerosis. Here, the recent progress of regenerative therapies using various somatic stem cells is described.

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INTRODUCTION

Pluripotent stem cells, which are capable of differentiating in various species of cells, are hoped to be donor cells in transplantation in regenerative medicine. Human embryonic stem (ES) cells[1] and induced pluripotent (iPS) cells[2] have the potential to differentiate in approximately all species of cells. However, the proliferating ability of these cells is high and the cancer formation ability is also recognized[2,3]. Ethical problems exist in using ES cells[4], while iPS cells produced from the patients themselves have little ethical problems. Gene transfer, particularly oncogene transfer, is associated with DNA change and cancer formation[2]. Omission of oncogene c-Myc from the defined four factors was tried and the cancer for-

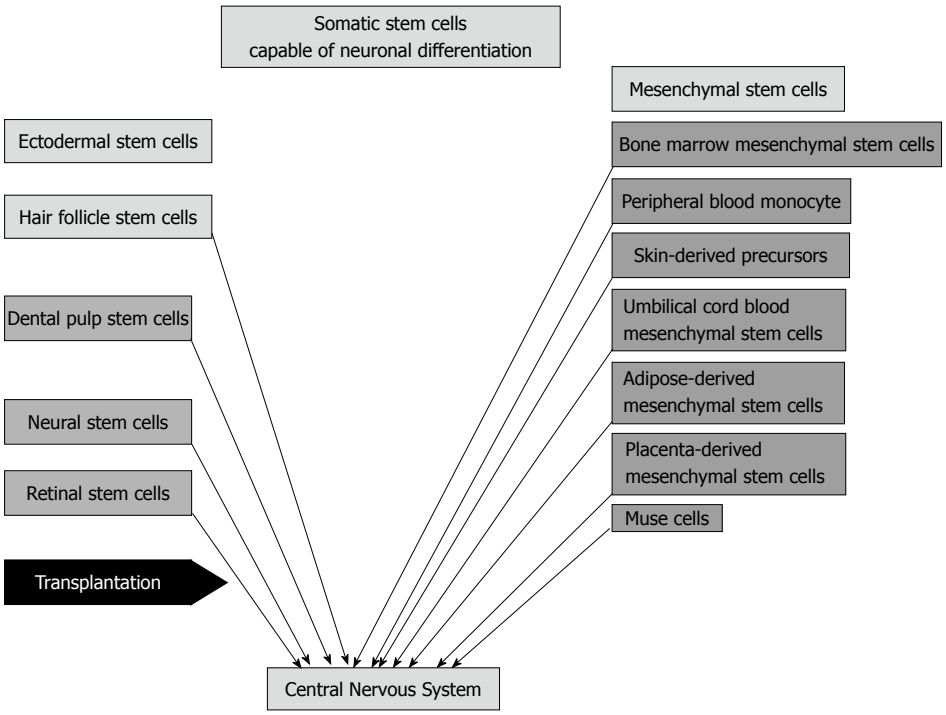

Figure 1 Somatic stem cells capable of neuronal differentiation. These cells are classified into two groups, ectodermal stem cells and mesenchymal stem cells. Ectodermal stem cells include hair follicle stem cells, dental pulp stem cells, neural stem cells and retinal stem cells, while mesenchymal stem cells include bone marrow mesenchymal stem cells, peripheral blood monocytes, skin-derived precursors, umbilical cord blood mesenchymal stem cells, adipose-derived mesenchymal stem cells, placenta-derived mesenchymal stem cells and Muse cells. These cells are candidates for donor cells for cell transplantation therapy for intractable neuronal diseases.

mation rate decreased[5]. In addition, no integration of defined factors into the genome was tried and brought good results[6]. However, cancer formation problems remain completely unsolved. It is probable that somatic stem cells reside in all organ tissues. In addition, truly pluripotent somatic stem cells, such as multilineage-differentiating stress enduring (MUSE) cells, are also probably harbored in all organ tissues[7,8]. However, it has been reported that the capability of neuronal differentiation is recognized in only mesenchymal or ectodermal stem cells[9,10]. Mesenchymal stem cells include bone marrow mesenchymal stem cells[11], adipose-derived mesenchymal stem cells[12], skin-derived precursors[13], umbilical cord blood-derived mesenchymal stem cells[14], placenta-derived mesenchymal stem cells, peripheral blood monocytes and MUSE cells[7], while ectodermal stem cells include hair follicle stem cells[15], dental pulp-derived stem cells[16], retinal progenitor/stem cells and neural progenitor/stem cells[17] (Figure 1). Although recent clinical trials of regenerative therapy for neuronal disease with transplantation of somatic stem cells has been performed with neural stem cells[18,19], bone marrow mesenchymal stem cells[20-25] and adipose mesenchymal stem cells[26], most of them stay at the level of confirmation of safety, but the efficacy of the therapies has not been shown (Table 1). On the other hand, numerous studies of transplantation of somatic stem cells using neuronal disease models have been reported and most studies have confirmed it to be efficient for the repair of neuronal diseases[27-34]. Ectodermal stem cells and mesodermal (mesenchymal) stem cells potentially differentiate to neurons, while it seems that endodermal stem cells do not differentiate to neurons without dedifferentiation or induction to iPS cells. Being different from iPS cells, these stem cells do not basically transform or dedifferentiate to cancer cells. The clinical application of somatic stem cells has a greater advantage than iPS cells. The regenerative effect of transplantation of somatic stem cells is considered to be mostly derived from trophic factors secreted from somatic stem cells. It is reported that the transplantation effect of adipose-derived stem cells is greater than bone marrow mesenchymal stem cells because the former cells secrete more vascular endothelial growth factor (VEGF) or hepatocyte growth factor (HGF) than the latter[35]. To survive as functional cells appropriate in the niche, it is necessary that transplanted cells differentiate to appropriate cells or somatic stem cells differentiate to appropriately functional cells before transplantation[36]. Naïve somatic stem cells scarcely differentiate to appropriate cells in the niche. Therefore, for example, it is necessary that transplanted somatic neuronal cells in the nervous system are differentiated to neuronal cells. Here, I describe regenerative therapy for neuronal diseases with transplantation of somatic stem cells.

NEURAL STEM /PROGENITOR CELLS

It is difficult to obtain human neural stem/progenitor cells but they are easily obtained from human fetal brains without ethical problems. The use of these human cells is

Table 1 Clinical applications of somatic stem cells in the treatment of neuronal diseases

Kind of cell	Disease	Ref.
Neural stem cell	Pelizaeus-Merzbacher disease	[19]
	Neuronal ceroid lipofuscinosis	[18]
Bone marrow mesenchymal stem cell	Alzheimer's disease	[58]
	Parkinson's disease	[20,59,60]
	Amyotrophic lateral sclerosis	[61-71]
	Multiple sclerosis	[21,22]
	Cerebral infarction	[57,73,74]
	Spinal cord injury	[23-25,77,78]
Adipose mesenchymal stem cell	Parry-Romberg syndrome	[26]

accompanied with a great ethical problem[37,38]. Previously, tissues of striatum and substantia nigra richly containing dopaminergic neurons were obtained from human fetal brain and were implanted into the striatum of Parkinson's disease patients. As a result, symptoms of a part of Parkinson's patients dramatically improved[39,40]. However, these clinical trials were stopped due to the difficulty of obtaining fetal brain tissue and a great ethical problem in using an abortion fetus. Neural stem cells reside in the subventricular zone and hippocampus. It is more difficult to obtain autologous cells from the brain. Therefore, transplantation of autologous neural stem cells has not been tried for neuronal regeneration. In addition, few clinical applications of allogenic transplantation of human neural stem cells have been performed[41,42].

In place of transplantation of human neural stem cells, activation of endogenous neural stem cells using fibroblast growth factor 2 (FGF-2), epidermal growth factor (EGF), erythropoietin and brain derived neurotrophic factor have been investigated[41,42]. Murine or rodent neural stem/progenitor cells are frequently used for regenerative research. Transplantations of neural stem/progenitor cells have been used for a Parkinson's disease model[36], cerebral infarction model[43], spinal cord injury model[27], retinal disease model[44] and so on. However, transplantation of neural stem/progenitor cells without treatment is not useful for regeneration of neural tissue because non-treated neural stem/progenitor cells cannot survive in the recipient's neural tissue and in addition cannot differentiate to a neuron[36]. Before transplantation, treatment of neuronal differentiation is effective for survival as a neuron. The addition of neurotrophic factors such as FGF8, sonic hedgehog and glial cell line-derived neurotrophic factor leads to neuronal differentiation[45]. In addition, gene transfer to cells is useful for neuronal differentiation in neural stem/progenitor cells. Gene transfers of Math-1[46], Ascl-1[47], Nurr-1[48] and von Hippel-Lindau (VHL)[49] show neuronal differentiation in neural stem/progenitor cells. Neuronal differentiation of intracellular transfer of protein or peptide is also reported. Intracellular transfer of VHL peptide, consisting of an amino-acid sequence of binding sites to elongin C, is useful for neuronal differentiation in neural progenitor cells (Figure 2). VHL peptide linked with protein transduction domain peptide shows high efficacy and rapid intracellular transduction. Transplantation of VHL peptide-treated neural stem cells promoted recovery in injured rat spinal cord[27]. Clinical applications using human allogenic neural stem cells have been tried for neuronal ceroid lipofuscinosis[41] and Pelizaeus-Merzbacher disease, both of which are hereditary intractable neuronal diseases[42] (Table 1).

RETINAL PROGENITOR /STEM CELLS

Recently, retinal progenitor/stem cells (RSCs) have been identified in not only embryonic and newborn retina but also in adult ciliary epithelium (CE) of rodents and humans[50-54]. Their niche has been suggested to be in the pigmented or nonpigmented epithelial layer of the ciliary margin at the peripheral edge of the retina. Since the majority of the differentiated cells were photoreceptor cells[54], transplantation of RSCs has shown their potential as tools for cell replacement in retinal degenerative diseases.

BONE MARROW MESENCHYMAL STEM CELLS

Bone marrow mesenchymal stem cells are also called bone marrow stromal cells and have been reported to be able to differentiate cells of bone, cartilage, adipose tissue, liver and neural tissue[55]. Transplantation of the bone marrow mesenchymal cells has been applied for cerebral infarction[56,57]. These cells are transplanted via intravenous transfusion and a part of them have been demonstrated to penetrate the blood brain barrier (BBB), but these penetrated cells scarcely survive and function as neurons in the brain[56,58]. Even if these cells do not differentiate to neural cells in the brain, these cells secrete neurotrophic factors which may have effects on neural tissue repair[58]. When the bone marrow stromal cells are transferred with the gene of Notch intracellular domain and neurotrophic factors were added, these cells mostly differentiated to neurons[55]. Clinical application with transplantation of bone marrow mesenchymal stem cells to neuronal degenerative disease patients of Alzheimer disease[57], Parkinson's disease[20,59,60], amyotrophic lateral sclerosis[61-71] and multiple sclerosis[21,22] have been tried, but those effects have not been fully established. Those induced neurons are transplanted to cerebral infarction model rats into the brain and the major part of the transplanted cells differentiated to neurons and the symptoms of the model rats improved[72]. VHL peptide-transferred bone marrow stromal cells partially differentiate to neurons and transplantation of those induced neurons improved the behavior of the spinal cord injury rats[28]. Human autologous bone marrow-derived mesenchymal stem cells have been transfused to brain ischemic disease patients[73,74]. The results of the clinical trials appear to be feasible and safe and occasionally an improving effect is observed. Several human clinical applications for spinal

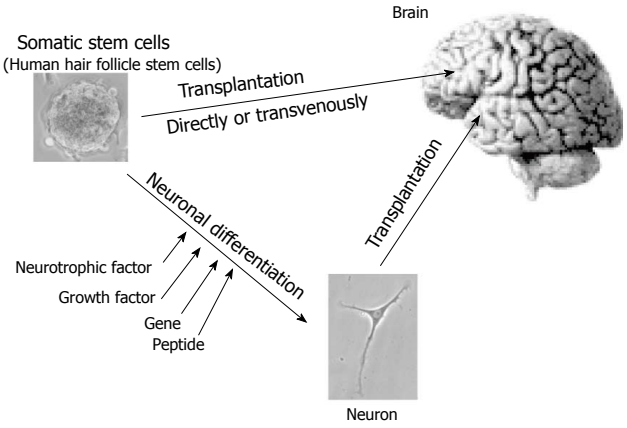

Figure 2 Transplantation of somatic stem cells into the central nervous system. Somatic stem cells (human hair follicle cell cells) forming a neurosphere, non-treated or neuronally differentiated by various methods, are directly or transvenously transplanted to brain.

cord injury with transplantation of bone marrow mesenchymal stem cells have been reported[23-25,72-78] (Table 1). Among them, improvement of motor function and electrophysiological findings have been recognized[25].

SKIN-DERIVED PRECURSORS AND HAIR FOLLICLE STEM CELLS

Skin-derived precursors (SKPs), which are also called dermal papilla stem cells, are reported to differentiate into various types of cells, including neuronal cells[79-81]. Although these cells are considered to originate from mesenchymal tissue in dermis, they differentiate to not only mesenchymal-derived cells, such as smooth muscle cells and adipose cells, but also epithelial lineage cells, such as neurons, glia and keratinocytes. In addition, nestin-expressing hair follicle stem cells residing at the hair follicle bulge region in mice and at the outer root sheath of hair follicle beneath sebaceous glands in humans are reported to differentiate to epithelial lineage cells, including neuronal cells[82,83], and they are also called neural crest stem cells [84]. These cells might contribute to neuronal regenerative therapy, repairing not only peripheral nerves but also the central nervous system, including brain and spinal cord[85,86] (Figure 2). It is reported that VHL peptide-transferred rodent SKPs were transplanted into cerebrum in Parkinson's disease rat models and they differentiated to dopaminergic neurons in the cerebrum with improvement of their symptoms[29,30]. This report suggested that SKPs are hopeful sources of donor cells to transplant into the nervous system for neuronal regenerative therapy.

ADIPOSE TISSUE-DERIVED MESENCHYMAL STEM CELLS

Adipose tissue-derived mesenchymal stem cells are similar to bone marrow-derived mesenchymal stem cells. These cells differentiate to various types of cells, derived from not only mesenchymal organs but also epithelial and endogenous organs. Recently, directed differentiation of motor neuron cell-like cells from human adipose-derived stem cells was induced with retinoic acid and sonic hedgehog[87,88], and the potential application for Huntington's disease or intracerebral hemorrhage is promising[89,90]. The application to animal models and also the human clinical application have been tried using those cells, but their human clinical application is still limited[91]. It is reported that adipose-tissue derived mesenchymal stem cells secret trophic factors, such as VEGF and HGF, which contribute to repair for ischemic brain tissue[35].

UMBILICAL CORD BLOOD-DERIVED MESENCHYMAL STEM CELLS

Human umbilical cord blood contains hematopoietic stem cells and mesenchymal stem cells. Umbilical cord blood-derived mesenchymal stem cells (UCBSCs) differentiate to neuronal cells and are clinically promising as a regenerative cell therapy for neuronal disease. It reported that neuronal differentiation of UCBSCs is mediated by protein kinase and that estrogen stimulates the neuronal differentiation of human UCBSCs[92,93]. UCBSCs differentiated to dopaminergic neurons *in vitro*. Transplantation of those cells is applied to neuronal disease models[94,95].

DENTAL PULP STEM CELLS

Dental pulp stem cells (DPSCs) are putatively neural crest cell-derived[96] and thus differentiate to neurons[97]. Therefore, these cells are promising as donor cells of neuronal regenerative cell therapy. Transplantation of DPSCs is applied to neuronal disease models such as spinal cord injury[98]. It is suggested that implanted adult human dental pulp stem cells induce endogenous axon guidance[99]. In addition, it is suggested that human DPSCs differentiate towards functionally active neurons in an appropriate environment[16].

PLACENTA-DERIVED MESENCHYMAL STEM CELLS

Placenta-derived mesenchymal stem cells are from mesenchymal somatic stem cells and differentiate to cells of neuronal phenotype in the appropriate niche conditions[100]. These cells differentiate to dopaminergic neuron-like cells *in vitro*[101]. In addition, intracerebral transplantation of these cells has been reported[102]. The transplantation of placenta-derived mesenchymal stem cells is promising for regenerative therapy for intractable neuronal diseases.

PERIPHERAL BLOOD MONOCYTES

Peripheral blood monocytes include mesenchymal stem

cells that are multipotential and capable of differentiating to neuronal lineage cells. These cells have the advantage of being obtained from an easily accessible minimally invasive procedure. With treatments of macrophage colony-stimulating growth factor and thereafter NGF, these cells express neuron specific enolase, neurofilament and microtubule associated protein 1-B that are neuronal markers[103]. These cells differentiate to microglia that is supportive for neuronal tissue[104] and are promising candidates as donor cells of autologous transplantation for neuronal regeneration.

MULTILINEAGE-DIFFERENTIATING STRESS ENDURING CELLS

Multilineage-differentiating stress enduring (MUSE) cells are pluripotent stem cells resembling ES or iPS cells[105]. These cells are derived from skin fibroblast or mesenchymal stromal cells[7,106]. Among stress (long-time heparin treatment) enduring fibroblasts, multilineage-differentiating stem cells were found. It is reported that these cells can differentiate to tri-dermal cells[7]. They are promising as donor cells for regenerative cell therapy[8]. Since they differentiated to neural lineage cells such as neuron and glia, they are hoped to be donor cells for neuronal regenerative cell therapy[107]. MUSE cells are the most promising somatic stem cells and the obtaining method is established. The autologous transplantation of MUSE cells obtained from autologous fibroblast or mesenchymal stem cells is useful for neuronal regenerative cell therapy. The necessity of cell sorting using anti-SSEA-3 antibody is a limiting factor in generating MUSE cells[7]. However, since the generative rate of MUSE cells is small but stable, use of MUSE cells is very promising as donor cells of transplantation of cell therapy for regeneration of neuronal disease.

ENDODERM-DERIVED SOMATIC STEM CELLS

Endoderm-derived somatic stem cells capable of neuronal differentiation are rare. When normal thyrocytes are cultured in non-serum small airway growth medium (SAGM) and their neuronal differentiation is induced, they express neuronal marker beta-III-tubulin[108]. This result suggests that thyroid cells derived from endoderm are capable of differentiating to neurons. Although direct conversion of hepatocytes derived from endoderm to neurons using defined factors has been recently reported[109], it is a report using a reprogramming method like iPS cells. Principally, it is likely that endoderm-derived stem cells are difficult to differentiate to neurons.

CONCLUSION

Cell transplantation therapy using somatic stem cells is very promising. At present, the kinds of clinically used somatic stem cells are mostly limited to neural stem cells and bone marrow mesenchymal stem cells. Other somatic stem cells are scarcely used for clinical applications. However, therapeutic levels of somatic stem cell therapy still mostly stay at the confirmation of safety and feasibility. Undoubtedly, neuronal regenerative therapy with transplantation of somatic stem cells will be applied to intractable neuronal diseases and spread throughout the world in the future.

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