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**Regenerative therapy for neuronal diseases with transplantation of somatic stem cells**

**Kanno H**. Neuronal regeneration with somatic stem cells

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**Abstract**

Pluripotent stem cells, which are capable to differentiate various species of cells, are hoped as donor cells in transplantation of regenerative medicine. Embryonic stem (ES) cells and induced pluripotent stem cells have potential to differentiate 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 having ability to differentiate various species of cells have been used as donor cells for neuronal disease 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, contribution to neuronal regeneration using non-treated somatic stem cells was poor, and various differential trials such as addition of neurotrophic factors, gene transfer, peptide transfer for neuronal differentiation of somatic stem cells have been performed. Here, recent progress of regenerative therapies using various somatic stem cells are described.

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

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

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**INTRODUCTION**

Pluripotent stem cells, which are capable to differentiate various species of cells, are hoped as donor cells in transplantation of regenerative medicine. Human embryonic stem (ES) cells[1] and induced pluripotent (iPS) cells[2] have potential to differentiate 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 problem, but gene transfer, particularly oncogene transfer, is associated with DNA change and cancer formation[2]. Omission of oncogene c-myc from defined four factors was tried, and cancer formation rate was decreased[5]. In addition, no integration of defined factors into genome was tried and was brought about 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 also probably harbor in all organ tissues[7,8]. However, it has been reported that capability of neuronal differentiation is recognized in almost only mesenchymal or ectodermal stem cells[9,10]. Mechenchymal stem cells includes 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 includes hair follicle stem cells[15], dental pulp-derived stem cells[16], retinal progenitor/ stem cells, and neural progenitor/stem cells[17] (Figure 1). Although recently 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 the safety, but the efficacies of the therapies have 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 been confirmed to be efficient for repair of neuronal diseases[27-34]. Ectodermal stem cells and mesodermal (mesenchymal) stem cells are 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. As regards, clinical application of somatic stem cells has greater advantage than iPS cells. 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 transplantation effect of adipose-derived stem cells is greater than bone marrow mesenchymal stem cells, because the former cells more secrete vascular endothelial growth factor (VEGF) or hepatocyte growth factor (HGF) than the latter cells[35]. To survive as functional cells appropriate in the niche, it is necessary that transplanted cells differentiate to appropriate cells or somatic stem cells are differentiated 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 fetus brains if without ethical problems. The use of these human cells is accompanied with a great ethical problem[37,38]. Previously tissues of striatum and substantia nigra richly containing dopeminergic neurons were obtained from human fetus brain, and they were implanted into striatum of Parkinson’s disease patients. As the results, symptoms of a part of Parkinson’s patients dramatically improved[39,40]. However, these clinical trials were stopped due to difficulty to obtain fetus brain tissue and a great ethical problem to use abortion fetus. Neural stem cells reside in subventricular zone and hippocampus . It is more difficult to obtain autologus cells from the brain. Therefore, transplantation of autologous neural stem cells has not been tried for neuronal regeneration. In addition, few clinical application of allogenic transplantation of human neural stem cells has been performed[41,42].

In place of transplantation of human neural stem cells, activation of endogeneous neural stem cells using has been fibroblast growth factor 2 (FGF-2), Epidermal growth factor (EGF), erythropoietin, and brain derived neurotrophic factor, 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 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 mostly useful for regeneration of neural tissue because non-treated neural stem / progenitor cells cannot mostly survive in recipient’s neural tissue and in addition cannot mostly differentiate to neuron[36]. Before transplantation, treatment of neuronal differentiation is effective for survive as neuron. 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[48], 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 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 the 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 human[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 as 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[57,58]. These cells are transplanted via the intravenous transfusion, and a part of them have been demonstrated to penetrate blood brain barrier (BBB), but these penetrated cells scarcely survive and function as neuron in the brain[56,57]. Even if these cells do not differentiated to neural cells in the brain, these cells secrete neurotrophic factors which may have effects neural tissue repair[56]. When the bone marrow stromal cells are transferred with gene of Notch intracellular domain and neurotrophic factors were added, these cells mostly differentiate to neurons[55]. Clinical application with transplantation of bone marrow mesenchymal stem cells to neuronal degenerative disease patients of Alzheimer disease[58], Parkinson 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 differentiate neuron and the symptom of the model rats improved[72]. VHL peptide-transferred bone marrow stromal cells partially differentiate to neurons, and transplantation of those induced neuron 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]. These results of the clinical trials appear to be feasible and safe, and occasionally improving effect is observed. Several human clinical applications for spinal 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 has been recognized[25].

**SKIN-DERIVED PRECURSORS AND HAIR FOLLICLE STEM CELLS**

Skin-derived precursors (SKPs), which are called as dermal papilla stem cells as another term, are reported to differentiate into various types of cells including neuronal cells[79-81]. Although these cells are considered to be originated 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 neuron, glia, and keratinocyte. 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 called as neural crest stem cells as another name[84]. These cells might contribute to neuronal regenerative therapy repairing not only peripheral nerve but also 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 as source of donor cells to transplant into nervous system for neuronal regenerative therapy.

**ADIPOSE TISSUE-DERIVED MESENCHYMAL STEM CELLS**

Adipose tissue-derived stem cells 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 organ but also epithelial and endogenueous 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 potential application for Huntington disease or intracerebral hemorrhage is promising[89,90]. Not only the application to animal models but also the human clinical application have been tried using those cells, 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 under appropriate environment[16].

**PLACENTA-DERIVED MESENCHYMAL STEM CELLS**

Placenta-derived mesenchymal stem cells are ones of mesenchymal somatic stem cells, and differentiate to cells of neuronal phenotype in the appropriate niche conditions[100]. These cells differentiate to dopaminegic 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 would be promising for regenerative therapy for intractable neuronal diseases.

**PERIPHERAL BLOOD MONOCYTES**

Peripheral blood monocytes include mesenchymal stem cells that are multipotential and capable to differentiate to neuronal lineage cells. These cells have the advantage to be obtained from an easily accessible with a minimal invasive procedure. With treatments of macrophage colony-stimulating growth factor and thereafter NGF, these cells express and 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 cell or iPS cells[105]. These cells are derived from skin fibroblast or mesenchymal stromal cells[7,106]. Among stress (long-time heparin treatment) enduring fibriblasts, multineage-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 as donor cells for neuronal regenerative cell therapy[107]. MUSE cells are the most promising somatic stem cells and the obtaining methods is established. The autologous transplantation of MUSE cells obtained from autologous fibroblast or mesenchymal stem cells would be useful for neuronal regenerative cell therapy. Necessary of Cell sorting using anti-SSEA-3 antibody is a limited factor in generating MUSE cells[7]. However, since generative rate of MUSE cells is small but stable, use of MUSE cells would be 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 to differentiate 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 with somatic stem cells are very promising. At present, kinds of clinically used somatic stem cells are mostly limited to neural stem cells and bone marrow mesenchymal stem cells. The other somatic stem cells are scarcely used for clinical applications. However, therapeutic levels of somatic stem cells therapy still mostly stay at the confirmation of safety and feasibility. Undoubtedly, neuronal regenerative therapy with transplantation of somatic stem cells will be usually applied to intractable neuronal diseases and spread in the world and in the future.

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**Figure 1 Somatic stem cells capable of neuronal differentiation.** Those 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. Those cells are candidates of donor cells for cell transplantation therapy for intractable neuronal diseases.



**Figure 2 Transplantation of somatic stem cells into 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.

**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 disease | |  | [58] |
|  |  |  |  |
| Parkinson disease | |  | [20,59,60] |
|  |  |  |  |  |  |
|  |  | Amyotrohpic lateral sclerosis | | | [59-71] |
|  |  | Multiple sclerosis | |  | [21,22] |
|  |  |  |  |  |  |
|  |  | Cerebral infaction | |  | [57,73,74] |
|  |  |  |  |  |  |
|  |  | Spinal cord injury | |  | [23-25,77,78] |
| Adipose mesenchymal stem cell | | Parry-Romberg disease | |  | [26] |
|  |  |  |  |
|  |  |  |  |
|  | | |  |  |  |