

## Stem Cell-Based Therapy in Human Neurodegenerative Diseases

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Cell therapy is a procedure in which replace healthy cells to unhealthy and damaged cells. Due to lack of suitable methods for treatment of neurological diseases, patients have problems enormous. The lack of neurotransmitters and neurotrophic factors are main causes of these diseases. During the past decade, a variety of cells such as embryonic stem cells, fetal-derived neuronal cells, and induced pluripotent stem cells (iPSCs) have been used for compensate neurological deficits and treatment of these disorders in a variety of animal models. Several studies have been conducted to produce nerve cells by different types of stem cells. Although researchs in this field has progressed, their use is somewhat limited due to ethical problems and possible formation of teratoma. In this paper, we reviewed methods used of stem cells for the treatment of neurological disorders.

**Key word:** Cell Therapy, Neurological Diseases, Embryonic Stem Cells, Ipscs, Teratoma.

Millions of people in worldwide are affected to neurological diseases. These diseases can occur due to neuronal death or dysfunction in certain areas of the brain, for example; in Huntington's disease loss of medium spiny neurons in the striatum<sup>1</sup>. Stem cells have three characteristics: non-specific cells, proliferation of large, high ability to become for cell types that lead to a lot of attention to their for treatment<sup>2</sup>. Stem cells for the first time have been identified in 1960 using [3H] -thymidine autoradiography labeling in the dentate gyrus of the brain in rodents<sup>3,4</sup>. Cells used for cell therapy should have important features: the availability of plenty, no

Immunogenicity, genetic stability and ability to differentiate, these features not only in adult or fetal neural stem cells but also seen in other types of stem cells such as mesenchymal stem cell (MSC)<sup>5</sup>. In line with our recent studies on cancer therapy in human ovarian cancer cell line (A) and human promyelocyticleukemia (NB-4) cells (B) in the present research, we studied Stem Cell-Based Therapy in human Neurodegenerative Diseases<sup>2-6</sup>. There are several method for use stem cell , such as stem cell with gene therapy, in this method replace gene deficit to gene health, stem cell with biomaterial, stem cell transplantation or infusion to peripheral blood and transplantation bone marrow stem cell<sup>7</sup>.

### Parkinson Disease

Parkinson's disease is the second most common neurological diseases and seen in patients muscles rigid, slow movements and mental disorders<sup>8</sup>. Although using transcription factors

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Nurr1 and Lmx1a can be formed DA neurons from embryonic stem cells but this method has been used only in animal models and studies have been not performed on human embryonic stem cells<sup>9</sup>. Neural stem cells and iPSC is good tool for knowledge and understanding of factors important that leads to loss of DA in Parkinson's disease<sup>10</sup>. Transplantation BM-MSCs in the SVZ brains of patients with Parkinson's disease lead to improve speech skill, fatigue and muscle thickening in these patients, also was found that these symptoms in patient who were in the early stages more than those who were in the final stages<sup>11</sup>. For absorption 6-OHDA need to dopamine active transporters (DAT), that absence of this transporter causes 6-OHDA in to other pathways and leading to disruption in there. also Plays a role in apoptosis through pathway dependent 6-OHDA in mdNSCs, but the transfer of hMSCs to secrete factors that inhibits apoptosis in neurons that could be a new therapeutic approach<sup>12</sup>. A research team examined that transplantation embryonic stem (ES) cells into striatum of mice through differentiate to DA neurons is highly effective in improving behavioral disorders<sup>13</sup>. When ES cells were transplantation into mice at first becoming midbrain neural stem cells and then differentiate to dopamine neurons that lead to improve electrophysiological and cognitive behavioral<sup>14</sup>. When transplanted human umbilical cord Wharton's Jelly into hemiparkinson rats, improved rotational behavior without tumor formation in brain that confirms safety of this type of stem cell for therapeutic goals<sup>15</sup>. The iPS cells due to the lack of immune response can be a useful tool for the treatment Parkinson's disease. Several studies have been shown that transplantation of these cells into brain in animal models of Parkinson's to differentiate into dopamine neurons can improve the disease's symptoms<sup>16</sup>.

### **Alzheimer Disease**

Alzheimer is an age-related disease that most prevalent among elderly. AD due to accumulation of insoluble plaques amyloid beta and neurofibrillary tangles (NFTs) in the regions of brain such as basal forebrain, amygdala, hippocampus, and cortical that lead to neuronal death<sup>17, 18</sup>.

Future efforts for remedy Alzheimer's can develop in animal models of Alzheimer by stem cells, such as human pluripotent stem cells (hPSCs)

for investigate neurotoxic agents in specific neuronal or BM-MSCs for examine tau hyperphosphorylation and stimulating microglial<sup>19,20</sup>. In one study was shown that use of stem cell-mediated prehension of neprilysin (A $\beta$ -degrading enzyme) is very useful in reducing amyloid plaques and increased synaptic density in both 3xTg-AD and Thy1-APP transgenic mice<sup>21</sup>. Can be used to induced pluripotent stem cells (iPSCs) from familial and sporadic AD patients created models of Alzheimer and they were treated with various compounds. A research group produced iPSCs with amyloid precursor protein (APP) -E693" mutation, and then they found that this mutation results in endoplasmic reticulum (ER) oxidative stress and oxidative stress and treatment with DHA dose reduction oxidative stress<sup>22</sup>. Transplantation of BM-derived mesenchymal stem cells (MSCs) into brains of Alzheimer's mice lead to that release of CCL5 and activation of microglia, they also demonstrated that microglia through release of neprilysin and interleukin-4 destroyed amyloid plaques<sup>23</sup>. Results of other studies show those transplantation intravenously or intracerebrally adipose-derived stem cells (ASCs) to Tg2576 mice improve memory and reduce the neuropathy<sup>24</sup>.

### **Amyotrophic Lateral Sclerosis**

ALS or Lou Gehrig is an neurological disorder undergoing causing destruction of motor neurons incerebral cortex, brain stem and spinal cord. About %5 to %10 are non-genetic disruption called familial; fALS, and the rest are sporadic (sALS)<sup>25</sup>. Several studies have performed different differentiation types of stem cells into motor neurons, for example, to generate motor neurons from iPS cells, we can understand mechanism of disease, examine the role of environmental factors and their interactions with other cells. In addition, transplantation of human marrow stromal cells (hMSCs) can reduce the activity of microglia and TNF $\pm$  secretion which consequently reduces inflammatory response in SOD1 transgenic mice<sup>26, 27, 28</sup>. Previous studies have indicated transplantation of human fetal spinal neural stem cells (hNSCs) into lumbar spinal cord of SOD1G93A rats improved  $\pm$ -motoneuron<sup>29</sup>. Previous studies have proven that olfactory ensheathing cell (OEC) transplantation appears to be able to slow the rate of clinical progression after OEC transplantation

in the first 4 months and cell intracranial and/or intraspinal (damaged segments) implants provide profit for patients (containing both the bulbar onset and limb onset subtypes) with amyotrophic lateral sclerosis (ALS). The cell therapy in patients with ALS is on the basis of long-term observation following multiple transplants. Furthermore, studies have shown that multiple doses of cellular therapy can certainly treat ALS<sup>30</sup>. Marconi *et al* showed that the administration of adipose-derived mesenchymal stem cells (ASC) into SOD1-mutant mice induces the release of basic fibroblast growth factor (bFGF) and glial-derived neurotrophic factor (GDNF) which in turn decreases ALS symptom<sup>31</sup>. Martinez *et al* isolated  $2.5-7.5 \times 10^5$  stem cells from ALS patients by leukapheresis technique, then transplanted them into the cerebrospinal fluid. They showed the procedure is safe and also can prevent disease progression<sup>32</sup>. Studies show that administration cord blood is a good method for remedy ALS. Administration of about  $10^6$  human umbilical cord blood (hUCB) cells into brain increases expression Nestin, III Beta-Tubulin and GFAP as markers neuron and microglia and prevent from disease progression<sup>33</sup>.

### Huntington's Disease

Huntington disease is a progressive neurological disorder that characterize by tremors, cognitive and emotional disorder. Its prevalence is Approximately 30,000 prevalence in the United States<sup>34</sup>. Pre-implantation Huntington gene (HTT) into multiple human embryonic stem cell lines obtained from blastocysts can be considered as a therapeutic method<sup>35</sup>. Also for understanding

disease mechanisms and treatment can be used to induce pluripotent stem cells (iPSCs) or MSC as vehicle for transmission of neuronal growth factors<sup>36</sup>. For example, using RNA interference (RNAi) can reduce expression mutant HTT and combine RNAi and stem cell given the high potential can be useful for treatment HD<sup>37</sup>. The use of human embryonic stem cell (hESC) for treatment of HD is very promising because it reduces %90 of mHTT soluble monomeric and greatly inhibit toxicity caused of them<sup>38</sup>. A research group newly presented the characteristics of a HD patient-derived iPSC carrying 72 CAG repeats (HD72-iPSC). Transplanted HD72-iPSC-derived neural precursors formed GABAergic neurons effective, but no EM48-positive protein aggregates were found at 12 weeks after transplantation<sup>39</sup>. A research group reports production and characterization of 14 induced pluripotent stem cell (iPSC) lines from HD patients and controls. Microarray analysis confirms that sequence CAG-repeat length correlates with pattern expression gene and as sequence CAG-repeat length varies in these patients result in electrophysiology, metabolism, and cell adhesion, are different in these cell lines obtained. It can be also used to these cells for screening<sup>40</sup>. In a study was to compare the efficiency of transplants of MSCs, aNSCs, or cotransplants of MSCs and aNSCs for decreasing deficits in a transgenic rat model of HD. The result illustrated that transplant of: (a) aNSCs produced a strong immune response and conferred short-term behavioral benefits; (b) MSCs elicited a relatively weak immune response, and provided a longer term behavioral benefit; and (c) combined MSCs and aNSCs conferred long-term behavioral benefits and incremented survival of the transplanted aNSCs. The finding that cotransplanting MSCs with aNSCs can lengthen aNSC survival and provide greater behavioral sparing than when the transplants contains only aNSCs suggests that MSCs are able to of creating a more suitable microenvironment for aNSC survival<sup>41</sup>. HTT gene mutations lead to changes in the immune system and increase inflammatory cytokines and chemokines such as interleukin-6, interleukin-10, CXC chemokine ligand 1 and interferon- $\gamma$  in serum patient with HD. In a study, transplantation bone marrow stem cells (BMSC)

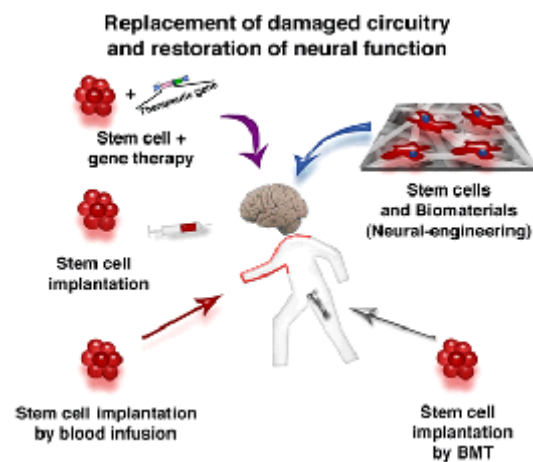


Fig. 1. Methods of cell therapy to stem cells<sup>7</sup>

into transgenic mice model of HD that express full-length htt (YAC128 and BACHD mice lead to reduce significantly levels of cytokines and chemokine<sup>42</sup>. MSC's role as carrier of RNAi was examined in a study, and Western blot and densitometry analysis showed that MSC expressing shRNA antisense to HTT were capable to reduce levels of mutant HTT expressed in both U87 and SH-SY5Y target cells<sup>37</sup>.

### DISCUSSION

Stem cells are useful tools for understanding molecular mechanisms and explore pathway that leads to neurological diseases. Although the use of stem cells for treatment of neurological disease is promising, these techniques are not still used widely. Before accepting these approaches as a tool for treatment, several issues should be resolved. Different types of stem cells are available for generation of neurons including NSCs, the MSCs, Wharton's jelly stem cell and induced pluripotent cells (iPS cells); however, the main issue is the risk of tumor formation as well as determining the most appropriate candidate for each disease is of the main issues for development of stem cell based techniques question which one is more suitable for treatment?

The use of iPSC cellular models can probably develop novel insights into the pathogenesis of neurodegenerative disorder and to help discover new drugs for its treatment and/or prevention. These models are derived from individual patients; the cellular characteristics can be relevant to clinical features of the disease in that patient.

However, the transgene integration and alteration of the endogenous genomic organization could cause reduction safety when considering medical applications. In conclusion, despite the promising results of stem cell applications for cell therapy in neurodegenerative disorder, it may be impeded by ethical problems and potential risk of teratoma formation.

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