



Resurrection of neurodegenerative diseases via stem cells

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Abstract— Neurodegenerative diseases (NDDs) are complex disorders that degenerates central nervous system. To this end, we have achieved only palliative treatments and their success is limited. Emerging studies suggest stem cells could be an alternative to recover lost neural network. Transplanting stem cells for replacing damaged neurons is a pivotal step in cell replacement therapies. In this article, NDDs and their pathology, current methods of combating NDDs and potentiality of stem cells in treating NDDs have been reviewed briefly. In addition to this, technical issues that hamper clinical applications of stem cells in creating cellular models and grafted cells for neuron resurrection have been discussed.

Keywords: Neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, Frontotemporal lobar degeneration, Amyotrophic lateral sclerosis, Induced Pluripotent cells

INTRODUCTION

Neurodegenerative diseases (NDDs) are devastating disorders with complex etiology. Loss of neurons in the central nervous system, which leads to dementia/ataxia or both is the characteristic feature of NDDs (Sanchez-Mut et al., 2016; Uttara et al., 2009). The pattern in which they occur slightly vary from disease to disease, yet all ultimately culminate to the progressive degeneration of neurons. However, the mechanism which commences this degradation is not clear. Many neurodegenerative diseases are characterized by the aggregation of misfolded/abnormal proteins, along with fibril formation and depositions. The **Figure 1** shows the diseases in NDDs and observed pathological proteins (**Fig. 1**).

These diseases are inexorable and there is a need for exigent solution for this crisis. Inefficacy of present treatments which are solely symptomatic, necessitate alternative approaches to combat with higher efficiency and to provide long term solution.

Phenomenal properties of stem cells and possibility of applications in regenerative medicine, encourages patient-oriented studies in neurodegenerative diseases. Stem cells are considered as cellular models to investigate disease pathology as well as transplantable grafts to recover, to ameliorate and to protect nervous system becomes intriguing research (Abud and Blurton-Jones, 2016; Haston and Finkbeiner, 2016; Wojda and Kuznicki, 2013).

This article aims to address recent advances of stem cells in NDDs for developing disease models and repairing neuron loss. This article will serve as primer to understand potential of stem cells in neurodegenerative resurrection. However, for deep insights on pathology and treatment methodologies, further reading on cited articles is inevitable. Among various neurodegenerative diseases, this article will focus on Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis and Frontotemporal lobar degeneration.

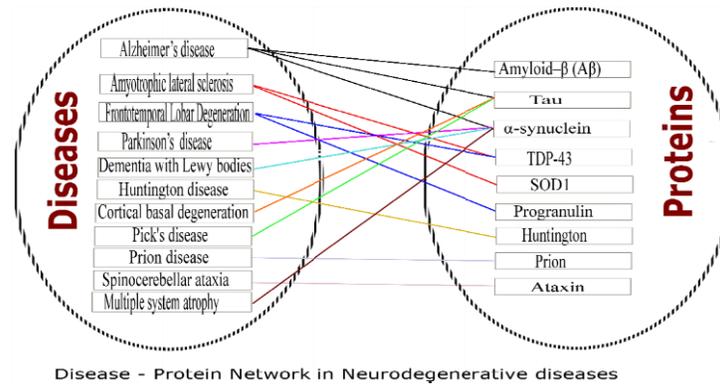


Figure 1. Pathological proteins in NDDs.

NEURODEGENERATIVE DISEASES (NDDs)

Alzheimer's disease (AD): It is the most common and prevalent NDDs. In 2015, 46.8 million people reported to have dementia, out of which over 60 percent of dementia are due to AD (Prince et al., 2016) 5% of AD are Familial AD (FAD) and over 95 % of AD are Sporadic AD (SAD) (Hunter et al., 2013). AD is characterized by the degeneration of neurons in basal forebrain, amygdala, hippocampus and cortical area, culminating in perceivable declination of memory and other cognitive functions such as thinking, understanding and attention (Whitehouse et al., 1981). Formation of amyloid- β peptide ($A\beta$) plaques and neurofibrillary tangles (Waldau and Shetty, 2008) are ideal hallmarks of the disease. Drugs inhibiting formations $A\beta$ plaques and neurofibrillary tangles are used in symptomatic treatment.

Parkinson's disease (PD)

Parkinson's disease is the second most common cause of progressive NDDs. Worldwide, 10 million people are affected by PD (http://www.pdf.org/en/parkinson_statistics.2013). PD is characterized by the degeneration of nigrostriatal dopaminergic neurons (Dimberger and Jahanshahi, 2013). Extensive degeneration of dopaminergic neurons results in programmed cell death, viral infection and accumulation of environmental toxins (Lang and Lozano, 1998). Hallmarks of pathogenesis are protein mis-folding and dysfunction of ubiquitin proteasome pathway. Lewy bodies formation occurs with α -synuclein and ubiquitin. Symptoms include bradykinesia, rigidity, resting tremor and postural instability. It is also associated with non-motor symptoms (Dauer and Przedborski, 2003).

Frontotemporal lobar degeneration (FTLD) and Amyotrophic lateral sclerosis (ALS)

Frontotemporal lobar degeneration (FTLD) and Amyotrophic lateral sclerosis (ALS) are most commonly overlapping neurodegenerative diseases. FTLD is a non-Alzheimer form of dementia characterized by either abnormal behavioral or aphasic patterns in people under the age of 65 years (Neary et al., 1998). FTLD can be sporadic or familial. FTLD can occur independently or with combination of amyotrophic lateral sclerosis, Parkinson's disease and with other neurodegenerative diseases (Ratnavalli et al., 2002). Amyotrophic lateral sclerosis is a neurodegenerative motor neuron disease. It is also called as Lou Gehrig's disease. It affects both upper and lower motor neurons. Upper motor neuron degeneration signs are hyperreflexia, extensor plantar response, increased muscle tone and weakness in topographic representation, while lower motor neuron degeneration signs comprise of weakness, muscle wasting, muscle cramps, fasciculation's and hyporeflexia. Regardless of initial symptoms, it eventually results in muscle atrophy and weakness (Hardiman et al., 2011). Death occurs within 3 to 5 years of diagnosis. Only 10% of ALS is familial, while 90% is sporadic. Genetic reasons for ALS still remain unclear (Al-Chalabi et al., 2012).

FTLD and ALS are caused as a result of dysfunction of many proteins. Origin of these neuro-degenerative diseases are multifactorial, among the numerous proteins such as Tau, Tar DNA binding (TDP-43) protein and Fused in Sarcoma (FUS) protein dysfunctions are observed commonly in both FTLD and ALS. Biological properties of these proteins are different in normal and diseased conditions. For instance, in healthy people TDP-43 is localized in the

nucleus and it plays a role in transcriptional regulation, pre-mRNA splicing, microRNA processing and mRNA transport (Buratti, 2008). Contradictorily, in FTLD and ALS patients, TDP-43 proteins are present as aggregates in the cytoplasm.

Stem Cells in NDDs

Cells that possess the property of self-renewal and differentiation to multiple cell types are called stem cells. Stem cells are classified into the following types based on their ability to differentiate.

- 1) Totipotent stem cells, that differentiate to any type of cell (e.g. Embryonic four cell stage)
- 2) Pluripotent stem cells, that differentiate to many cell types (e.g. Embryonic stem cells)
- 3) Multipotent stem cells differentiation are limited to few cell types (e.g. Adult stem cells)

Induced Pluripotent cells (iPSCs). These cells are non pluripotent cells (somatic cells) which are induced to become pluripotent. This induction via regulating transcription factors such as *Oct4*, *Sox2*, *Klf4* and *c-Myc*(Eminli et al., 2008; Okita et al., 2007; Wernig et al., 2007)

Embryonic stem cells (ESCs), Mesenchymal stem cells (MSCs) and Induced pluripotent stem cells (iPSCs) are transformed to neuronal progenitor cells (NPCs) or neuronal stem cells (NSCs) from which several neuronal lineages are obtained based on specific differentiation. Upshot is that, reprogramming the cell to various neuronal lineage to correct neurodegenerative diseases. Manipulating expression of the transcription factors will convert fibroblast cells to neuronal cells. Factors such as *Ascl1*, *Brn2*, and *Myt11in* (Pang et al., 2011) and *Mash1*, *Ngn2*, *Nurr1* and *Ptx3* in (Liu et al., 2012) reported to reprogram the cells to neuronal cells.

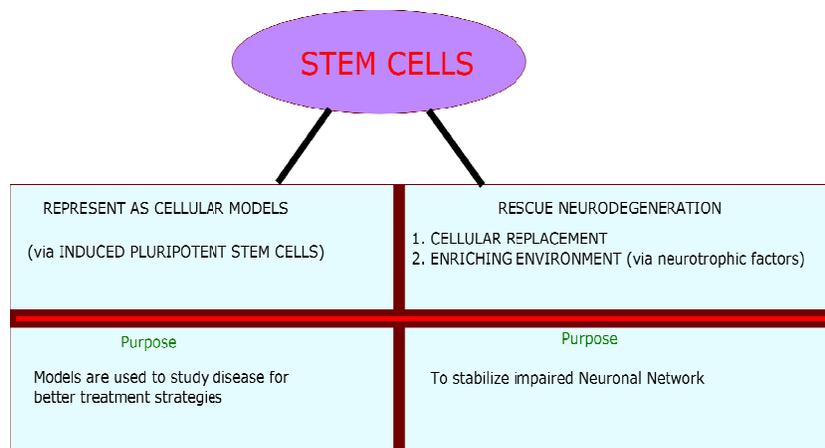


Figure 2. Application of stem cells in NDDs.

Induced pluripotent stem cells were used in developing cellular models. iPSCs were used to create models for AD (Israel et al., 2012) PD (Woodard et al., 2014), ALS (Egawa et al., 2012) and Huntington’s disease (Juopperi et al., 2012). These models assist in understanding the pathological changes occurred during the disease progression. These changes could be of phenotypic or sub cellular observations (Swinney and Anthony, 2011). Apart from developing cellular models, stem cells are used in two ways to treat neurodegenerative diseases. In first place, stem cells are “Necessary cell population” in transplanted affected region, where it is intended to replace the complete functionality of degenerated

neurons. Secondly, stem cells are used as “Auxiliary cell population” to serve as a source to induce other cells via promoting the secretion of neuroprotective growth factors such as brain-derived neurotrophic factor (BDNF), glial-derived neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1) (Medvedev et al., 2010; Suzuki and Svendsen, 2008; Xuan et al., 2008). **Figure 2** shows the application of stem cells in NDDs (**Fig. 2**).

Representative studies of currently available studies in treating NDDs and potentiality of stem cell in treating NDDs have been tabulated in **Table 1**.

Table 1. Representative studies in NDDs treatments

Major studies	Studies attempted via stem cells
Alzheimer's disease (AD)	
<p>Cholinesterase inhibitor drug, Memantine- a N-methyl-D-aspartate (NMDA) receptor blocker and neuron protecting factors reported to ameliorate AD (Roberson and Mucke, 2006). Other studies reported usage of β secretase inhibitors (Golde, 2003) γ secretase inhibitors (Li et al., 2000) A β Vaccination (Schenk, 2004) Non-steroidal anti-inflammatory drugs (NSAIDs) (Weggen et al., 2001) Cholesterol lowering drug (Puglielli et al., 2003) Clioquinol, metal-protein attenuating compound (Cherny et al., 1999) and Glycosaminoglycans-mimetics in ameliorating AD (Geerts, 2004).</p>	<p>Grafting of NSCs into the hippocampal regions in AD mouse improved cognition (Blurton-Jones et al., 2009). Human undifferentiated NSCs used for AD treatment in rats (Qu et al., 2001). Transplanted ES cells-derived neurospheres used for AD treatment in mouse (Wang et al., 2006). Human umbilical cord blood mononuclear cells used to treat AD in mice study (Ende et al., 2000). Bone marrow-derived adult progenitor cells (MAPCs) was used to ameliorate AD (Chen et al., 2006).</p>
Parkinson's disease (PD)	
<p>L-dopa (Lloyd et al., 1975) Monoamine oxidase-B (MAO-B) inhibitors (Youdim and Bakhle, 2009) Catechol-O-methyltransferase (COMT) inhibitors (Männistö and Kaakkola, 1990).</p> <p>Amantadine and anticholinergic agents (Schwab, 1969) Catecholamines (Conway, 2001) have been reported in PD studies.</p> <p>In drosophila, chaperones such as HSP 70 and drugs such as geldanamycin stimulate the activation of chaperones resulting in the prevention of the loss of dopaminergic neurons (Auluck, 2001).</p>	<p>Transplantation of human mesencephalic tissue ameliorated PD in a patient (Piccini et al., 1999). In rats, undifferentiated mouse embryonic stem cells used to form differentiated dopamine neurons (Bjorklund et al., 2002). In rats, ES cells to tyrosine hydroxylase positive (TH⁺) neurons, were produced to exudate dopamine (Kim et al., 2002). In primate model, stromal cell-derived inducing activity (SDIA)-treated monkey ES cells differentiated to dopamine releasing cells in combination with cytokine induction (Takagi et al., 2005). Bone marrow mesenchymal stem cells (MSCs) and undifferentiated human umbilical cord matrix stem cells (UCMS) were employed in treating PD in rats (Weiss et al., 2006). Human neural stem cells (hNSCs) implanted into 1-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP) treated PD primates (Redmond et al., 2007).</p>
Frontotemporal lobar degeneration (FTLD)	
<p>Microtubule stabilizing drugs (Lee et al., 1994).</p> <p>Tau filament and Tau phosphorylation inhibitors. LMTX, a methylene blue analog serves as tau and TDP-43 aggregation inhibitor (Wischik et al., 1996).</p>	<p>H9 cell line based (H9-ESC), and iPSCs were used for neuron generation to treat FTLD (Raitano et al., 2015).</p>
Amyotrophic lateral sclerosis (ALS)	
<p>Riluzole, glutamate release inhibitor used in ALS treatment (Miller et al., 2007). Antioxidants such as vitamin C and vitamin E are reported to ameliorate ALS (Orrell et al., 2005). Ciliary neurotrophic growth factor (CNTF) in (Bongioanni et al., 2004). Insulin-like growth factor I (IGF-I) in (Mitchell et al., 2007) reported to protect neurons from degeneration. Anti-inflammatory, anti-apoptotic, anti-glutamatergic, neuroprotective and antioxidant drugs showed promising (Zoccolella, 2009).</p>	<p>Homeobox gene Hb9 expression induces mouse ES cells to differentiate to cholinergic motor neuron (Wichterle et al., 2002). MSCs transplantation into the spinal cord to ameliorate ALS (Mazzini et al., 2006)</p> <p>In a mouse model, neurons obtained from human NT- 2 cell line (Garbuzova-Davis et al., 2002) and umbilical cord blood cells (Garbuzova-Davis et al., 2003) delayed the progression of ALS.</p>

CONCLUSIONS

Review by (Avior et al., 2016; Yamanaka, 2012) discussed pros and cons of application of pluripotent stem cells in disease modeling and disease rescuing approaches. **Figure 3** was drawn based on (Avior et al., 2016; Yamanaka, 2012) shows the limitations of pluripotent stem cells (**Fig. 3**). Also, the application of stem cells in the resurrection of neurodegenerative diseases is hampered by limited understanding in

- 1) Quantitative determination of fate of transplanted neuronal cells in integration, synaptic connection and recapitulating in the neuronal network remains unanswered.

- 2) Does introduced neurons into the brain cause tumorigenesis?
- 3) Does introduced neurons survive and reinnervate and what determines its efficacy?
- 4) To what extent axon has to grow in the affected regions and what regulates its migration are must to know information for effective stem cell based therapies.

To date, advancement in stem cell therapies in improving treatments in neurodegenerative diseases are promising. However, it is too early to vouch for stem cell based therapies in humans.

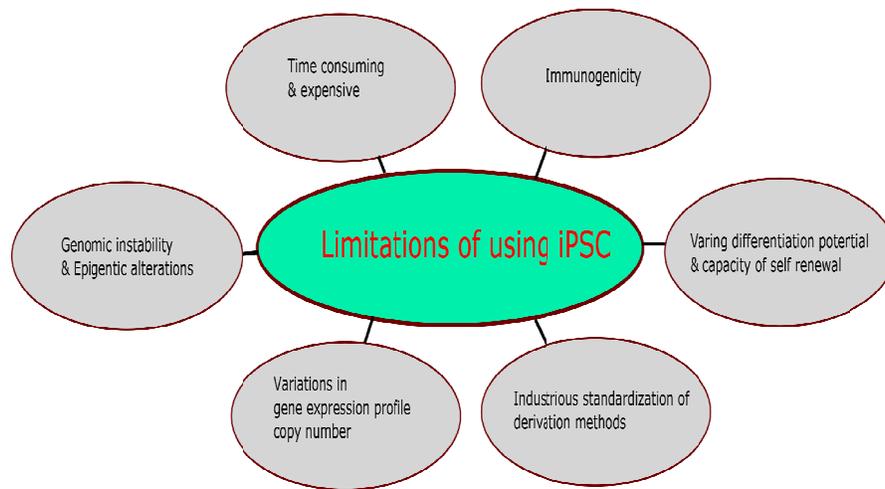


Figure 3. Limitations of iPSCs.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; BDNF: Brain-derived neurotrophic factor; CNTF: Ciliary neurotrophic growth factor; COMT : Catechol-O-methyltransferase; ESCs: Embryonic stem cells; FAD: Familial Alzheimer's disease; FTLD: Frontotemporal lobar degeneration; FUS: Fused in Sarcoma; GDNF: Glial-derived neurotrophic factor; hNSCs: Human neural stem cells; HSP 70: Heat shock protein 70; IGF-1: Insulin-like growth factor-1; iPSCs: Induced Pluripotent cells; L-DOPA: L-3,4-dihydroxyphenylalanine; MAO-B: Monoamine oxidase-B; MAPCs: Marrow-derived adult progenitor

cells; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSCs: Mesenchymal stem cells; NDDs: Neurodegenerative diseases; NMDA: N-methyl-D-aspartate; NSAIDs: Non-steroidal anti-inflammatory drugs; NSCs: Neuronal stem cells; PD: Parkinson's disease; SAD: Sporadic Alzheimer's disease; SDIA: Stromal cell-derived inducing activity TDP-43: Tar DNA binding protein- 43; UCMS: Umbilical cord matrix stem cells; VEGF: Vascular endothelial growth factor.

Competing interests

The authors declare that they have no competing interests.

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