Induced pluripotent stem cells as a potential treatment for Huntington’s disease

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Chapter outline

1. Huntington’s disease ................................................................. 50
2. HTT gene and protein function ................................................. 51
3. Epigenetics and HD ................................................................. 51
4. Signs and symptoms of HD ..................................................... 52
5. Stem cell therapy for HD .......................................................... 53
   5.1 Mesenchymal stem cells (MSCs) and HD.............................. 54
   5.2 Neural stem cells (NSCs) and HD .......................................... 54
   5.3 Embryonic stem cells (ESCs) and HD ................................. 55
6. Induced pluripotent stem cells (iPSCs) ...................................... 55
   6.1 Induced pluripotent stem cells (iPSCs) and HD ..................... 55
   6.2 iPSC-based therapy for HD .................................................. 56
      6.2.1 Transplantation of undifferentiated iPSCs for HD ............. 56
      6.2.2 Transplantation of differentiated iPSCs for HD ................ 57
7. Stem cells-based HD clinical trials ......................................... 59
8. Summary and conclusions ...................................................... 61
Acknowledgments ........................................................................ 62
References .................................................................................. 62

Abstract

Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder that usually affects middle-aged individuals, the median age of symptom onset is 42 years. HD is invariably fatal and the drugs that are currently available are only palliative. Of the many promising therapeutic approaches, genetic therapies and
especially reintroduction of genetically altered stem cells have gained considerable attention. Studies using stem cell therapies have evolved from using mesenchymal stem cells (MSCs), neural stem cells (NSCs), and embryonic stem cells (ESCs) to induced pluripotent stem cells (iPSCs). Since iPSCs have the ability to differentiate into any of the three mammalian germ layers, their use has become a promising new approach for cell replacement therapy, including their use for treating HD. Two therapeutic approaches using iPSCs for cell replacement include transplantation of undifferentiated iPSCs or using those that have undergone partial differentiation into a desired cell lineage. Very little is known about the relative efficacy of transplanting these two different types of iPSCs, especially with regard to treating HD. This chapter gives a brief overview of stem cell–based transplantation therapy in HD, with a major focus on what is currently known about the efficacy of undifferentiated versus partially differentiated iPSCs transplant therapy in HD. In addition, the novel idea of transplanting reprogrammed (i.e., gene-corrected) autologous cells from HD patients as a source of iPSCs is explored.

**Keywords:** Autologous transplantation; Cell differentiation; Degeneration; Differentiated iPSCs; Fibroblast; Gene correction; HD models; HD patients; HTT; Huntington’s disease; Induced pluripotent stem cells; Medium spiny neurons; Reprogramming; Transplantation; Undifferentiated iPSCs.

1. Huntington’s disease

Huntington’s disease (HD) is a fatal neurodegenerative disease that is inherited in an autosomal dominant pattern, affecting both males and females. HD is found globally with an incidence of six per 100,000 individuals. HD is a late-onset disease, usually occurring at the age of 40 years or above. The major underlying cause of the overt phenotypes of the disease first comes from neuronal degeneration in the caudate and putamen regions of the human brain. Other brain regions that undergo degeneration include the cortex, thalamus, and cerebellum (Ross and Tabrizi, 2011). The neurodegeneration in these regions primarily affects dopaminergic (DA), gamma aminobutyric acid (GABA), and glutamatergic neurotransmitter systems (Frank, 2014). The degeneration results from the aggregation of mutant Huntingtin protein (mHTT), formed by a polyglutamate tract encoded by cytosine—adenine—guanine (CAG) repeat expansions in exon 1 of the gene. The number of CAG repeats are negatively correlated with the age of onset. mHTT is insoluble, forming aggregates in cells that eventually become toxic, specifically mHTT accumulation in medium spiny neurons (MSNs) of the basal ganglia is the suspected cause of neuronal degeneration in this brain region. Patients with more than 37 CAG repeats are diagnosed as having HD (Roos, 2010). The elongated CAG repeats lead to toxicity in a gain-of-function manner. However, there is considerable evidence that there is a significant loss of function that also contributes to, and exacerbates, HD pathology (Paine, 2015).

Currently, there is no cure or effective treatment for HD. However, there are many potential drugs being considered, several of which are being tested in clinical trials. The only FDA-approved drug is tetrabenazine (TBZ), which is used to combat
the aberrant motor symptoms of HD. Although TBZ is effective in controlling the chorea-like symptoms of HD, some of the patients experience adverse side effects emanating from intolerance of TBZ. In addition to TBZ, new drugs such as deutetranbenazine, riluzole, and amantadine are being tested for controlling HD symptoms (Frank, 2014; Dean and Sung, 2018).

### 2. HTT gene and protein function

The human HD gene (HTT; formally known as IT-15) is one of the largest genes (325 kb) in humans and is located at chromosomal loci 4p16.3. HD exhibits an autosomal dominant inheritance pattern with 100% penetrance, equally affecting males and females (Myers, 2004). The HTT gene encodes for the 3144 amino acid HTT protein (348 kDa). The HTT protein is expressed ubiquitously, with the highest expression in such brain regions as the striatum, cerebellum, cortex, and hippocampus. Due to the association of the N-terminal region of the gene with HD, an area that encodes a specific toxic protein fragment, the N-terminus has been thoroughly characterized and studied. Nonetheless, the exact function of the entire HTT protein has yet to be fully elucidated, although some of the most commonly attributed functions include:

1. Interaction with huntingtin-associated protein (HAP) to aid anterograde and retrograde transport of organelles and cargo in the axons and dendrites of the neurons;
2. Cell division, as HTT is found in the mitotic spindle fibers in dividing cell types required for cell division;
3. Cellular processes such as endocytosis, endosomal trafficking, and vesicle recycling are also some of the major functions of HTT, following their interactions with certain proteins; and
4. Regulation of autophagy, leading to self-degradation of the aggregated mHTT in the cells (Saudou and Humbert, 2016; See Fig. 3.1).

### 3. Epigenetics and HD

Wild-type (WT) HTT, as well as mHTT, has a major role in upregulation and downregulation of genes by interacting with gene activators and repressors. Therefore, differential expression of certain genes leads to neuronal dysregulation, as well as the triad of symptoms (motor, cognitive, and psychiatric) that characterize HD. We have described the epigenetic basis of HD in detail in a previous publication (Srinageshwar et al., 2017), so this is not extensively covered in this chapter.

A key epigenetic interaction that deserves special attention is the role of HTT and mHTT in activating or deactivating the gene encoding brain-derived neurotrophic factor (BDNF). In general, BDNF plays a major role in maintaining neuronal activity and integrity, cell–cell signaling, and facilitating neurotransmitter release.
BDNF is also involved in different cell signaling pathways that are required to maintain normal cellular functions and metabolism. BDNF is dysregulated in HD as well as in Parkinson’s disease (PD), Alzheimer’s disease (AD), and multiple sclerosis (MS) leading to neuronal degeneration (Bathina and Das, 2015). Specifically, in HD, there are various histones (such as H3 and H4) that are either hypoacetylated or methylated at the BDNF promoter region, leading to reduced expression of the BDNF protein (Chen and Chen, 2017). Therefore, introduction of a BDNF-based therapy has been very popular and successfully used in HD translational research performed by many researchers, including us (Dey et al., 2010).

4. Signs and symptoms of HD

HD has a triad of symptoms including motor, cognitive, and psychiatric disturbances that characterize the disease (Fig. 3.2). The motor symptoms include chorea (dance-like, uncontrollable movements), jerkiness, rigidity, loss of coordinated voluntary movement and coordination. Choreic movement is considered the hallmark overt symptom of HD and its occurrence is commonly used to define the onset of HD. In HD, cognitive dysfunction emerges around 15 years prior to the onset of overt symptoms of the disease and worsens as the disease progresses. The cognitive symptoms include memory loss, attention and learning deficits, deficits in the speed of psychomotor processing, perseverative thinking, impairment in olfaction, and language difficulties. As these symptoms get worse, there is concomitant brain atrophy and decrease in key neurotrophic factors and growth hormones. Usually the cognitive assessment for HD is based on the Unified Huntington Disease Rating Scale (UHDRS); however, measures of mild cognitive impairment (MCI) have been developed to assess cognitive impairment in prodromal HD patients. Psychiatric
symptoms of HD are categorized into two types: (1) affective and (2) non-affective (Smith et al., 2000; Paulsen, 2011; Paoli et al., 2017). Affective symptoms include increasingly larger shifts in mood and can include behavioral outbursts and bouts of depression. Nonaffective symptoms often include disorders of thought, paranoia, and/or episodes of psychotic-like behavior.

5. Stem cell therapy for HD

Although early experimental transplant therapies for HD utilized fetal or embryonic stem cells (ESCs), more recent studies shifted to the use of adult stem cells, such as mesenchymal stem cells (MSCs), neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs; Fig. 3.3).

Due to the ethical controversies, propensity for rejection, and lack of availability, the use of ESCs for transplants has been slowly supplanted by the use of MSC, NSCs, or iPSCs. The degree to which any of these stem cells differentiate into the types of neurons needed to produce a significant cell replacement therapy is still controversial, although there is growing evidence that iPSCs show considerable promise to do so (Medvedev et al., 2010).

In any case, it is well documented that these stem cells have therapeutic potential, by either supporting or maintaining the existing healthy neurons through secretion of trophic factors. A brief description of how these different types of stem cell—based therapies are being used in translational research for treating HD is presented as follows.
5.1 Mesenchymal stem cells (MSCs) and HD

Mesenchymal stem cells/stromal cells (MSCs) are adult multipotent stem cells that have been widely used as a potential therapy for HD. The degree to which the MSCs can differentiate into functional neurons is highly debated, but their ability to provide critical trophic factors has been shown repeatedly (Rossignol et al., 2015). Given that the HD brain contains abnormally low levels of BDNF, making the host neurons vulnerable to apoptosis and excitotoxicity, it was hypothesized that MSCs transplants might restore BDNF levels and provide critical neuroprotection (Zuccato et al., 2011).

MSCs are known to secrete BDNF, which helps to create an optimal microenvironment for maintaining the neuronal integrity of the brain. We and others have transplanted MSCs derived from rodent bone marrow (BM) and umbilical cord (UC) into several rodent models of HD. In addition, we have also shown that MSCs, when genetically modified to overproduce BDNF, are highly therapeutic in transgenic YAC128 HD mice by alleviating the signs and symptoms of the disease (Dey et al., 2010; Fink et al., 2013). There are a variety of studies that have confirmed the therapeutic effects of MSCs and BDNF in HD (Olson et al., 2012; Rossignol et al., 2015; Pollock et al., 2016). A detailed description of MSC transplantation in HD can be found in our recent review (Srinageshwar et al., 2020).

5.2 Neural stem cells (NSCs) and HD

NSCs can be obtained from a specific region of the brain and can be easily expanded in culture and induced to differentiate into neurons. Transplantation of NSCs in different HD rodent models has proven to be highly advantageous, leading to very promising outcomes. The transplanted NSCs are able to integrate into the host tissue at the site of degeneration in the HD brain and either by repopulating the area of the lost neurons and/or preventing further neuronal loss and revitalizing vulnerable neurons so that motor function are improved, as well as enhancing the long-term...
5.3 Embryonic stem cells (ESCs) and HD

Although ethical issues continue to surround the use of ESCs, scientists have successfully used them to reduce symptoms in HD, and there is considerable evidence that ESCs are capable of differentiating into neural cells in the HD brain. One of the major advantages of using ESCs over other types of stem cells is that ESCs are not readily rejected by the immune system and are relatively safe, in terms of not inducing uncontrolled proliferation (Volarevic et al., 2018). Previous studies using the neurotoxic quinolinic acid (QA) rat model of HD showed that transplanting human ESC-derived neural stem cells into HD rats was therapeutic; the transplanted cells differentiated into neurons at the site of the QA-induced lesion in rats, leading to the reduction of behavioral deficits (Song et al., 2007). Similar results were obtained by transplanting human ESC-derived GABAergic neurons in QA-lesioned mice, leading to recovery from locomotor deficits (Ma et al., 2012). However, the ethical issues and availability of human embryos, as well as some residual concerns surrounding the long-term efficacy and safety of ESC transplants, have prompted researchers to explore using iPSCs transplants for HD.

6. Induced pluripotent stem cells (iPSCs)

As the name suggests, iPSCs are pluripotent stem cells that are capable of self-renewal, as well as differentiating into multiple lineages, giving rise to endoderm, ectoderm, or mesoderm germ layers. iPSCs were first cultured in 2007 by reprogramming somatic cells (skin fibroblasts) using specific factors, Oct4, Klf-4, Sox2, and c-Myc, popularly known as Yamanaka factors—OKSM. iPSCs are very similar to ESCs in terms of cell differentiation, proliferation, characterization, and genetic and epigenetic markers. The discovery of the means to produce iPSCs has enhanced stem cell-based research, and iPSCs are rapidly replacing ESCs in the pursuit of potential therapies for a number of diseases, including PD, AD, and HD, because researchers can now circumvent the ethical concerns associated with ESCs through the use of iPSCs, which still retain the ability to produce multiple cell lineages (Takahashi et al., 2007; Romito and Cobellis, 2016).

6.1 Induced pluripotent stem cells (iPSCs) and HD

iPSCs have critical advantages compared to any other cell types for stem cell-based therapy, as well as for disease modeling. Perhaps the most significant advantage of
iPSCs over other types of stem cells in cell replacement therapies is that the patient receiving the transplant can donate the iPSCs being transplanted. This ensures greater immunocompatibility and reduces the risk of rejection. Of course, in the case HD and other genetic disorders, an additional step of editing the mutated gene is required before the autologous transplant can be done. With the use of new gene-editing tools, such as CRISPR-Cas9, this procedure is now feasible and represents a novel concept and approach to iPSC transplantation for HD. The added advantage of iPSCs over ESCs (besides circumventing many of the ethical issues surrounding the use of human embryonic tissue) is the greater availability of iPSCs, since these can be produced readily from the patient’s own cells. Another major advantage of iPSCs over MSCs and NSCs is that iPSCs, like ESCs, have a greater propensity to utilize the biochemical cues of the transplant site environment and to differentiate into the type of region-specific neurons that are most needed for functional recovery (Liu et al., 2016).

6.2 iPSC-based therapy for HD

Use of iPSCs-based therapy for HD includes (1) transplantation of undifferentiated iPSCs or (2) transplantation of iPSCs that have been partially differentiated into the specific cell type most needed to compensate for the cells that have degenerated in the HD brain (Fig. 3.4). The following section will summarize the different strategies of iPSCs transplantation in HD and the therapeutic outcomes.

6.2.1 Transplantation of undifferentiated iPSCs for HD

Recently, Mu et al. (2014), (2016) transplanted iPSCs into the ipsilateral ventricle of a QA rat model of HD. The iPSCs migrated from the lateral ventricles to the lesioned

![FIGURE 3.4](image)

A representation of iPSC transplantation in HD.
striatum and differentiated into region-specific neurons. To assess the motor outcomes following treatment, behavioral tests were performed, which showed that the QA-lesioned rats receiving iPSC transplants recovered from the QA-induced motor deficits when compared to the untreated controls (Mu et al., 2014). A series of immunohistochemistry and protein assays revealed changes in the expression of a number of protein markers that correlated with the therapeutic outcome following iPSC transplantation. Some of the proteins that were upregulated include glia-derived neurotrophic factor, basic fibroblast growth factor, leptin, and other hormones known to regulate glucose. Most importantly, the inflammatory marker, cytokine-induced neutrophil chemoattractant-3, was downregulated, indicating reduced inflammation following iPSC transplantation (Mu et al., 2016).

Work in our lab utilized the reprogramming of rat tail-tip fibroblasts into iPSCs and then transplanted them into the striatum of rats that had been given the neurotoxin, 3-nitropropionic acid (3-NP; Fink et al., 2014), which induces HD-like neuropathology. Intrastriatal transplantation was done at different time points, corresponding to the early, middle, and late stages of HD. The accelerated rotarod task was used to assess the degree of recovery from 3-NP-induced motor deficits following transplantation. This study indicated that the iPSC transplants alleviated the motor deficits in rats receiving iPSC treatment at all stages. The rats that received the iPSCs at the early and intermediate stages of HD showed behavioral sparing on the rotarod task and the preservation of striatal metabolic activity, as well as protection against 3-NP-induced ventricular enlargement in the brain compared to untreated rats and those that received iPSC treatment at the later stages of HD. Importantly, the rats that received iPSC transplants during the period that mimicked the later stages of HD showed functional recovery on the accelerated rotarod task, in which their 3-NP-induced motor deficits were reversed by the iPSC treatment. In addition, some of the transplanted iPSCs differentiated into astrocytes around the transplanted region. Treatment at early and intermediate stages in this study also prevented much of the 3-NP-induced neuronal death compared to the rats that did not receive treatment and those receiving iPSC at a later time point. Impressively, immunohistochemical analysis provided evidence that some of the transplanted iPSCs differentiated into region-specific neurons. These results suggest that transplanting iPSCs during the early stages of HD may serve a neuroprotective role and preserve behavioral functioning and that iPSC transplants at later stages can actually restore some of the lost functions. However, the degree to which restoration of function is achieved may depend on the ability of the iPSCs to differentiate into region-specific neurons. This role of iPSC-induced recovery needs to be studied further (Table 3.1).

6.2.2 Transplantation of differentiated iPSCs for HD

Given that MSNs are a specific striatal cell population that degenerate early in HD, some researchers have focused on differentiating the iPSCs into MSN-like cells prior to transplantation. Carri et al. (2013) differentiated human iPSC cells into MSN progenitor cells that express the markers FOXG1, OTX2, and GSX2. Following terminal differentiation, these cells expressed DARPP-32, a protein marker that is
expressed by 95% of MSNs in the striatum. Further electrophysiological analysis showed that 57% of these cells achieved repeated firing and action potentials establishing their functionality in vitro. These cells were transplanted into the striatum of the QA-lesioned HD rats. The tissue was collected and analyzed at different time points showing the presence of the graft. During early stages following transplantation, the cells expressed only a few neuronal markers. However, by week 9 following transplantation, the transplanted cells expressed the DARPP-32 specific marker, indicating that the grafted cells were adopting the MSN cell fate. Further, the rats with the iPSCs transplant showed reduced apomorphine-induced rotations compared to the untreated QA rats (Carri et al., 2013).

Jeon et al. (2014) partially differentiated HD patient—derived iPSCs (72 CAG repeats) toward an medium spiny neuronal lineage by co-culturing them with PA6 stromal cells. Following this partial differentiation, these cells were bilaterally transplanted into the striatum of 12-month-old YAC128 mice and the rotarod task was used to assess functional outcome. Interestingly, even though the transplanted iPSCs retained their mHTT aggregates, the cells were therapeutic and improved the motor activity of the HD mice. Moreover, tissue analysis showed that the transplanted cells expressed neural precursor markers, including those that give rise to GABAergic cells and MSNs. However, the origin of the mHTT aggregates throughout the tissue is unclear, since mHTT is produced by both the transplanted iPSCs and the host tissue (Jeon et al., 2014).

Table 3.1 A summary showing the outcomes of transplantation of naïve iPSCs in HD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Agents/genes for reprogramming</th>
<th>HD model</th>
<th>Study outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu et al. (2014)</td>
<td>Healthy mouse fibroblast</td>
<td>Lentivirus</td>
<td>Quinolinic acid (QA) treated rats</td>
<td>Sparing of motor behavioral deficits</td>
</tr>
<tr>
<td>Mu et al. (2016)</td>
<td>Healthy mouse fibroblast</td>
<td>Lentivirus</td>
<td>Quinolinic acid (QA) treated rats</td>
<td>Increased expression of growth factors and neurotrophic factors that helps in maintaining neurons. Downregulation of inflammatory markers</td>
</tr>
<tr>
<td>Fink et al. (2014)</td>
<td>Healthy rat tail-tip fibroblast</td>
<td>Adenovirus containing Oct4, Sox2, Klf-4, and c-Myc</td>
<td>3-nitropropionic acid (3-NP) treated rats</td>
<td>Sparing of motor behavioral deficits and loss of neurons in the early and intermediate stages. Functional recovery after the late-stage intervention.</td>
</tr>
</tbody>
</table>
Another study from our lab used iPSCs that were derived from healthy adult mice and which were partially differentiated into induced neural stem cells (iNSCs). These iPSCs-derived iNSCs were then characterized using markers that are specific for cell differentiation into a neuronal lineage, including Nestin, Sox2, β-tubulin-III, and NeuN. Upon confirming the neuronal differentiation, the cells were transplanted bilaterally into the striata of YAC128 HD mice and measures of tissue pathology and behavioral improvements were made. Our results revealed that the HD mice given iPSC-iNSCs showed behavioral sparing, relative to vehicle-treated HD mice. Moreover, the histological analyses showed the presence of the transplanted cells in the striatum containing the phenotypic biomarker, DARPP-32, suggesting that they had differentiated into region-specific MSNs. There was also a significant increase in production of BDNF in the iPSC-iNSC-transplanted HD to vehicle-treated HD mice (Al-Gharaibeh et al., 2017).

As far as clinically relevant use of iPSCs therapy for HD, a critically important study was conducted by An et al. (2012), who used HD-iPSCs-derived NSCs as a cell replacement therapy. In this study, the HD cells underwent gene correction before partial differentiation into NSCs and MSNs lineages. These cells were transplanted into the striatum of QA-treated HD mice and the gene-corrected NSCs survived and fully differentiated into MSNs (An et al., 2012).

Similarly, Cho et al. (2019) differentiated WT- and HD monkey-derived iPSCs into neural progenitor cells (NPCs), which were then gene-corrected. Specifically, the HTT gene in the HD-iPSC-NSC cells was targeted using sh-RNA, which suppresses expression of the HTT protein and consequent aggregate production. Following this, the HD HTT gene-modified cells or WT cells were transplanted into N171-82Q HD mice. The study showed that the normal and the gene-corrected NPCs derived from iNSCs were able to survive in the striatum following transplantation and differentiated into site-specific neural cells and astrocytes. Moreover, these cells ameliorated the motor deficits as evidenced by performance on the rotarod task. In terms of survival, the mice that received the gene-corrected cells survived longer than the control groups. This study clearly shows that the mice receiving transplants of gene-corrected NSCs derived from iPSCs were able to survive and differentiate in the HD mouse brain at higher rates compared to the non-gene-corrected cells. Furthermore, mice given transplants of gene-corrected iPSCs exhibited preserved grip strength, motor performance on the rotarod test, and longer survival times than mice that were vehicle-treated and those transplanted with WT-derived iPSCs (Cho et al., 2019) (Table 3.2).

7. Stem cells—based HD clinical trials
Stem cells have been used in clinical trials for HD with some success (see Srinageshwar et al., 2020, for detailed descriptions). Most of the clinical trials in HD used fetal stem cells, but these studies produced mixed results, along with some adverse side effects. However, no clinical trials using pluripotent stem cells, specifically iPSCs,
Table 3.2 Summary of outcomes of studies using transplantation of differentiated iPSCs in animal models of HD.

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Agents/genes for differentiating iPSCs</th>
<th>Differentiated cell type</th>
<th>HD model</th>
<th>Study outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carri et al. (2013)</td>
<td>HD patients</td>
<td>Neural induction media</td>
<td>iPSCs differentiated to medium spiny neuron progenitor cells</td>
<td>Quinolinic acid (QA)-treated HD rats</td>
<td>Transplanted cells survived, differentiated into MSNs, and reduced apomorphine-induced rotations</td>
</tr>
<tr>
<td>Jeon et al. (2014)</td>
<td>HD patient</td>
<td>Neural induction media</td>
<td>HD iPSCs differentiated into neural precursor</td>
<td>YAC128 HD mice</td>
<td>Transplanted cells survived, differentiated, and reduced behavioral deficits</td>
</tr>
<tr>
<td>Al-Gharaibeh et al. (2017)</td>
<td>Healthy mouse tail-tip fibroblast</td>
<td>Neural induction media</td>
<td>iPSCs differentiated into neural stem cells</td>
<td>YAC128 HD mice</td>
<td>Transplanted cells survived, differentiated, and reduced behavioral motor deficits</td>
</tr>
<tr>
<td>An et al. (2012)</td>
<td>Commercially purchased</td>
<td>Embryoid body method</td>
<td>Gene-corrected HD iPSCs differentiated into neural stem cells</td>
<td>Quinolinic acid (QA)-treated HD rats</td>
<td>Transplanted cells survived, differentiated into MSNs</td>
</tr>
<tr>
<td>Cho et al. (2019)</td>
<td>HD and WT monkeys</td>
<td>Neural induction media</td>
<td>HD (corrected with sh-RNA) and WT iPSCs differentiated into neural progenitor cells</td>
<td>N171-82Q HD mice</td>
<td>Transplanted cells survived and reduced behavioral deficits and increased longevity</td>
</tr>
</tbody>
</table>
have been conducted for HD. A persistent fear is that production of iPSCs often involves oncogenes, such as c-Myc, which could potentially result in the production of tumors by the transplanted cells. Another potential drawback for clinical testing on HD patients involves whether the advantages of autologous iPSCs transplantation would be lost because such transplants would entail the use of iPSCs that contain mHTT. However, as discussed in this review, these shortcomings may be surmountable as there is growing evidence that iPSCs do not appear to produce tumors and the use of gene-corrected iPSCs would circumvent the risk of initiating more problems by autologous transplants in HD patients.

8. Summary and conclusions

Although only a few studies have been conducted using iPSCs as a potential cell replacement therapy for HD, there are two emerging approaches: (1) transplanting undifferentiated iPSCs or (2) transplanting partially differentiated iPSC that may readily give rise to the specific type of neurons or other cells needed to enhance therapeutic outcomes. Although the use of partially differentiated iPSCs makes sense when it is known what the specific type of replacement cells are needed to be, the use of undifferentiated iPSC may be more appropriate for situations in which the specific type of replacement cell that is needed is unknown or when several cell types need to be replaced so that relying on the brain microenvironment to signal which types of cells are needed may work best. Clearly, further research is needed to better understand the complexities of the brain microenvironment, but as this knowledge emerges, inducing a specific defining cell lineage prior to transplantation may provide greater efficacy in terms of promoting recovery. As further research using iPSCs to treat HD unfolds, the promise of safely using iPSCs to effectively treat HD may soon be realized.

Critical to the use of iPSCs for treating HD is whether autologous transplantation of the cells obtained from HD patients is feasible. Although early work in this area is encouraging, whereby no adverse effects following transplantation of human HD cells in HD mice were observed (Jeon et al., 2014), autologous transplantation in a clinical setting may require correction of the mHTT gene of the iPSCs prior to transplantation (Fig. 3.5). However, unlike for some other neurological or CNS injuries in which time is a critical factor for generating sufficient amounts iPSCs, use of iPSCs for treating HD is relatively less time-sensitive. For time-sensitive treatments, allogeneic transplantation may be a viable option, especially as the iPSC-based technology for cell replacement therapy improves (Ohnuki and Takahashi, 2015).

As new research on the use of iPSCs for HD emerges, a clearer understanding of whether transplanting undifferentiated or partially differentiated iPSCs would provide more optimal outcomes or whether transplanting gene-corrected autologous or allogeneic cells would be more effective should be easier to address. Encouragingly, the early work in this emerging field suggests that stem cell treatment for HD is a very promising approach to combat this devastating disease.
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References


CHAPTER 3  Induced pluripotent stem cells as a potential tool for Huntington’s disease


