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Induced Pluripotent Stem Cells in Huntington's Disease: Disease Modeling and the Potential for Cell-Based Therapy

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Abstract

Huntington's disease (HD) is an incurable neurodegenerative disorder that is characterized by motor dysfunction, cognitive impairment, and behavioral abnormalities. It is an autosomal dominant disorder caused by a CAG repeat expansion in the *huntingtin* gene, resulting in progressive neuronal loss predominately in the striatum and cortex. Despite the discovery of the causative gene in 1993, the exact mechanisms underlying HD pathogenesis have yet to be elucidated. Treatments that slow or halt the disease process are currently unavailable. Recent advances in induced pluripotent stem cell (iPSC) technologies have transformed our ability to study disease in human neural cells. Here, we firstly review the progress made to model HD in vitro using patient-derived iPSCs, which reveal unique insights into illuminating molecular mechanisms and provide a novel human cell-based platform for drug discovery. We then highlight the promises and challenges for pluripotent stem cells that might be used as a therapeutic source for cell replacement therapy of the lost neurons in HD brains.

Keywords

Huntington's disease; Induced pluripotent stem cells; Stem cell models; Drug discovery; Cell replacement therapy

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by abnormal expansion of triplet CAG repeats in the *huntingtin* gene (*HTT*), which encodes an expanded polyglutamine (polyQ) stretch in the huntingtin protein (Htt) [1]. This toxic mutant protein (mHtt) leads to progressive and prominent degeneration of the GABAergic projection neurons in the striatum and ultimately more widespread loss of other brain regions [2]. Typically, HD manifests at a mean age of 40 years, with death occurring 15–20

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Conflict of Interest The authors declare that they have no competing interests.

years from the onset [3]. It is characterized by distinct clinical features, including chorea, dystonia and parkinsonism, cognitive decline, and behavioral abnormalities [3]. HD shows a stable prevalence of approximately 5–7 diseased individuals per 100,000 among most Caucasian populations, with many more people at risk of the disease [1, 4]. HD is fully penetrant when individuals carry 40 or more CAG repeats, while incomplete penetrance happens with 36–39 repeats [5]. Mutations between 28 and 35 CAG repeats show instability during paternal inheritance [1, 5]. Although the causative gene and mutation was identified more than 20 years ago, the precise pathophysiological mechanisms by which this mutation leads to degeneration of the target neurons and disease onset remain elusive. Presently, there is no effective disease-modifying treatment to delay or halt the fatal progression of disease, and current management is aimed primarily at the alleviation of symptoms [6].

Recently, a revolutionary discovery by Yamanaka et al. has demonstrated that mouse and human fibroblasts could be reprogrammed into self-renewing pluripotent cells displaying many properties of embryonic stem cells (ESCs) by retrovirally introducing four specific transcription factors (Oct3/4, Sox2, Klf4, and c-Myc) [7, 8]. Oct3/4 proves to be the most important factor, the expression of which is highly specific for pluripotent stem cells and cannot be replaced by other Oct family members to generate induced pluripotent stem cells (iPSCs) [9]. In contrast, the other three factors are expressed in other cells and can be replaced by other family members [10]. Sox2 is expressed in neural stem/progenitor cells and plays a vital role in repressing neuronal differentiation, but the forced expression of Oct3/4 rescues the pluripotency of Sox2-null ESCs [11, 12]. Klf4 is expressed in skin, stomach, intestine, and skeletal muscle, while c-Myc is ubiquitously expressed. Either c-Myc- or Klf4-deficient mice survive until birth, indicating that other factors compensate to maintain pluripotency [10]. In recent years, the breakthrough of iPSCs has promoted a tremendous increase in interest regarding the application of iPSC technology to regenerative medicine and human disease modeling [13]. In particular, iPSCs have shown great potential as a therapeutic strategy for incurable diseases of the central nervous system, ranging from brain cancers to neurodegenerative disorders, such as HD, Parkinson’s disease (PD), Alzheimer’s disease, and amyotrophic lateral sclerosis [14–17]. Here, we review the application prospects of iPSC technology in HD, focusing particularly on the use of iPSCs in disease modeling, drug discovery, and cell replacement therapy.

Neuropathology and Molecular Pathogenesis of Huntington’s Disease

The normal function of Htt remains poorly understood at present [18]. As a ubiquitously expressed and conserved protein across species, Htt is fundamental for post-implantation development and may play a significant role in normal functioning of the basal ganglia [19]. Wild-type Htt upregulates the transcriptional level of brain-derived neurotrophic factor (BDNF), which is particularly important for the survival and maturation of striatal neurons predominantly affected in HD [18, 20]. And the levels of BDNF protein and BDNF mRNA were found consistently reduced in HD striatum [20]. Although mHtt is expressed throughout the body, neuropathological alterations in HD are markedly selective, with prominent cell loss and atrophy in the caudate and putamen [21]. GABAergic medium-sized spiny neurons (MSNs) in the striatum are the most vulnerable [22]. Other brain areas significantly affected in HD patients include the cerebral cortex, hippocampus, substantia

nigra, thalamus, hypothalamus, and cerebellum [21]. Another hallmark pathological feature of HD is the appearance of inclusion bodies containing $mHtt^{+}$ aggregates [23]. Initial studies of HD brains reported inclusions mainly in the nucleus, while subsequent works also identified $mHtt^{+}$ aggregates in the cytoplasm and neuropil, even in extracellular matrix and blood vessels [24, 25].

The production of toxic mHtt protein has several pathophysiological consequences for the affected neurons in HD [3, 21]. By interacting with mitochondria, mHtt might impair oxidative metabolism and mitochondrial calcium handling, leading to reduced ATP levels, defective Ca^{2+} uptake, and enhanced oxidative stress [26]. Striatal MSNs are selectively vulnerable to the toxicity of excitatory amino acids, in particular glutamate and its analogues [27]. Importantly, mHtt expression alters excitatory synaptic activity in the striatum by reducing glutamate uptake and enhancing signaling at *N*-methyl-D-aspartate receptors [28]. The gene-expression profiles between postmortem human HD brains and animal models are remarkably comparable, supporting the idea that altered transcription is a crucial mechanism in HD pathogenesis [29, 30]. Expanded polyQ repeats enter the nucleus and mediate transcriptional dysregulation through their interaction with cellular transcription factors, which may ultimately induce neuronal dysfunction and cell death in HD [31–33]. Moreover, mHtt aggregates are produced continuously beyond the ability of cells to degrade these proteins by proteasome and autophagy pathways, resulting in increasing aggregate accumulation [34–38]. All these pathogenic mechanisms eventually lead to apoptotic or necrotic cell death, responsible for abnormal neuropathological features of HD [39].

Current Therapeutics for Huntington's Disease

Despite the fact that the HD gene was identified over 20 years ago, no curable therapy for the disease is currently available. The majority of current pharmacological therapeutics are solely symptomatic treatment of the dominant motor, psychiatric, and cognitive aspects of HD [40]. Tetrabenazine remains the only drug approved by the US Food and Drug Administration for the treatment of chorea associated with HD and has shown clear efficacy for reducing chorea, though it has a risk of potentially deleterious effects [41]. Antipsychotic agents, including olanzapine, haloperidol, risperidone, and clozapine, are used to treat patients with psychiatric/behavioral disturbances. Donepezil and rivastigmine are traditional therapeutics for enhancing cognitive function. In the past few years, there are a number of clinical trials designed to evaluate potential therapeutic agents, most of which target those aforementioned pathophysiological consequences that occur downstream of protein translation [42]. Several agents are in ongoing phase II/III trials such as cysteamine, resveratrol, pridopidine, laquinimod, and epigallocatechin gallate [6]. However, the majority of clinical studies to date have not demonstrated efficacy, although these agents have yielded promising results in preclinical models [6]. Given that HD is a monogenic disorder, novel approaches aimed at silencing or repairing the *mHTT* gene, such as antisense oligonucleotides (ASOs), RNA interference (RNAi), ribozymes, DNA enzymes, and genome-editing approaches, are becoming attractive therapeutic options [43]. These strategies directly interfere with the cause of the disease by targeting mHtt at the genomic or post-transcriptional level [44]. Several oligonucleotide-based approaches have been reported as potential allele-selective HD therapeutics [45, 46]. A phase 1/2a clinical study by Isis

Pharmaceuticals using ASOs in patients with early-stage HD has now initiated (NCT02519036). Several hurdles, such as off-target effects and lack of effective and nontoxic delivery systems, need to be overcome before these approaches can enter the clinic [43].

Modeling Huntington's Disease In Vitro with Patient-Specific iPSCs

Illuminating the molecular basis of HD and, ultimately, expediting the discovery of disease-modifying therapies that delay the onset and slow the progression of HD depend on reliable disease models [47]. Both chemically induced and transgenic animal models that recapitulate features of HD have enabled plenty of powerful avenues for research [47, 48]. However, traditional animal models may not be able to precisely mimic the disease process in human cells due to differences between species [49]. The majority of therapies that are effective in animals have failed in human clinical trials [50]. Furthermore, generating and breeding transgenic animals are costly and slow. Thus, a rapider and more human-relevant model system is required to advance research into the HD pathogenesis and drug discovery. The rapid development of iPSC technology opens exciting new opportunities to model HD in vitro with the ability to differentiate patient-derived pluripotent stem cells into susceptible neuronal subtypes.

iPSCs have prominent advantages over ESCs in some respects. First, iPSCs can be derived directly from skin cells of HD patients (Fig. 1), avoiding ethical concerns resulting from blastocyst destruction in the process of obtaining human ESCs [51]. Besides, iPSCs generated from individual patients would be a better source for cell replacement therapy than ESCs that would inevitably lead to immune rejection issues [52]. Furthermore, patient-derived iPSCs harbor all disease-associated genetic components that render GABAergic neurons susceptible to the disease. Therefore, they represent the most genetically precise model and might be helpful to further investigate genetic factors related to HD pathogenesis [53, 54]. Moreover, gene-silencing technologies based on patient-specific iPSCs may offer a way to correct this monogenic disorder, paving the road for personalized medicine [44, 55, 56].

In principle, in vitro disease modeling comprises differentiating control and disease-specific iPSCs/ESCs into GABAergic neurons and comparing these target cells for disease-relevant phenotypes [53]. To date, iPSC lines that have been generated from HD patients indeed exhibited robust pathologic phenotypes that replicate many features of this disorder (Table 1). The first study on the feasibility of reprogramming patient fibroblasts into iPSCs was reported by Park et al. [57]. However, initial phenotypic differences between HD-iPSC lines carrying 72 CAG repeats and controls were not significant. Afterwards, Zhang et al. reported an increase in caspase-3/7 activity in neural stem cells (NSCs) generated from HD-iPSCs upon growth factor withdrawal when subjecting iPSCs to a neuronal differentiation paradigm [58]. This group also observed mitochondrial dysfunction and decreased BDNF transcription upon growth factor deprivation in HD-iPSC-derived NSCs [55]. Another study revealed differentially expressed protein patterns in comparative proteomic analysis [59]. Specifically, a total of 26 upregulated oxidative stress-associated proteins and downregulated cytoskeleton-associated proteins were identified in HD-iPSCs at undifferentiated stages.

Furthermore, HD-iPSC lines exhibited more DNA damage-mediated apoptosis and reduced neuronal differentiation efficiency and neurite length [59]. Moreover, multiple molecular pathways that are characteristically dysregulated in HD were also present in undifferentiated pluripotent HD-iPSCs, including dysregulation of the MAPK and Wnt signaling pathways and altered expression of p53 [60]. Apart from iPSCs generated from aforementioned heterozygous *HTT* mutations, Camnasio et al. for the first time generated iPSCs from two homozygous HD individuals who carried *HTT* expansions between 39 and 44 CAGs, and observed enhanced lysosomal activity in HD-iPSCs and their derivatives. However, no distinguishable differences in reprogramming, growth rate, caspase activation, or neuronal differentiation were observed between normal and mutant genotypes [61].

In 2012, the HD Consortium reported a total of 14 iPSC lines derived from HD patients and controls, and uncovered a series of CAG-repeat-expansion-associated phenotypes [62]. Whole-transcript expression profiling revealed many transcriptional changes involved in signaling, cell cycle, axonal guidance, and neuronal development, which were consistent with previously described disturbances in HD pathogenesis. Furthermore, CAG-repeat-associated alterations in actin cytoskeleton, cell-cell adhesion, ATP/ADP levels, and electrophysiological properties have been observed in derived neural cells. Moreover, HD-derived lines exhibited increased susceptibility to cell stressors such as BDNF withdrawal and glutamate, which was verified by a more recent study in the juvenile-onset HD lines [62, 63].

Not only has the neuronal lineage derived from HD-iPSCs been intensively studied, an independent group has also differentiated iPSCs into an astrocytic lineage. Surprisingly, the diseased astrocytes displayed obvious cytoplasmic vacuolation that increased over time under fundamental conditions without additional stressors [64]. This finding was consistent with those seen in peripheral blood lymphocytes of HD patients [64, 65].

Although iPSC models have reproduced many features of HD, the spontaneous formation of $mHtt^{+}$ aggregates has not been observed in human iPSCs. A recent study indicated that treatment of in vitro culture with a proteasome inhibitor MG132 could induce mHtt aggregation in HD-iPSCs [66]. Interestingly, this group also observed $mHtt^{+}$ aggregates at 33 weeks after transplantation of HD neural progenitor cells (NPCs) into rat brains, suggesting that additional stressors and cellular age may be key factors in developing protein aggregates in human HD-iPSCs.

The endogenous HD mutations persist in all cell types. Almost all neural cells derived from HDi PSCs contain the same CAG expansion as the parental fibroblasts, and the size of CAG repeats did not augment during the course of reprogramming, long-term growth in vitro, and neuronal differentiation [58, 61]. The HD Consortium indicated that the normal and expanded CAG repeat alleles exhibited only slight instability upon differentiation for most of the HD-derived lines [62]. One line displayed complete stability of the short allele; however, the long CAG repeat increased to 118 from 110 after 26 passages of NSCs [62].

Creation of iPSC lines from patients with this monogenic disorder not only allows experiments on disease phenotypes in vitro but also opens an opportunity to repair gene

defects *ex vivo*. An et al. reported that HD-iPSCs could be corrected by replacement of the expanded CAG repeat with a normal repeat using homologous recombination, and the correction persisted in differentiated MSNs in vitro and in vivo [55]. In order to improve the efficiency of recombination, they extended this work by adopting a CRISPR based genome-editing approach [67].

Using Human iPSC Lines for Drug Discovery

Despite the fact that the causative gene for HD has been identified for more than 20 years, current therapeutics available to HD patients are mainly palliatives and disease-modifying therapies have not yet been established [41]. Development of new drugs is an expensive and time-consuming process, while the majority of drug candidates that are efficacious in animals have failed in clinical trials due to safety and efficacy issues [68]. The final goal of in vitro disease modeling with human pluripotent stem cells is to find better therapeutic targets and more effective drugs that would benefit a large number of patients. A recent study used human ESC/iPSC-derived dopaminergic neurons as a platform to screen a group of compounds as potential neuroprotective agents in PD [69]. Of the 44 compounds known to work in rodent systems, only 16 showed neuroprotection in neurotoxin-induced dopaminergic cell models, highlighting the importance of using disease-relevant human neurons for such assays [69]. iPSCs offer numerous advantages over the traditional methods in drug discovery. This human model may eventually reveal how mHtt triggers molecular events that ultimately result in motor, cognitive, and behavioral disturbances of HD patients. Recently, a particular interest has been focused on the discovery of small molecules that are able to inhibit the toxic effects of mHtt and attenuate neurodegeneration [70]. Human iPSC-based models have the potential as power tools for high-throughput drug screening, bioinformatics, and global gene-expression analyses, accelerating the pace of drug discovery and reducing drug attrition rate [49, 71].

Furthermore, patient- and disease-specific iPSCs have the potential for indicating mutation-triggered molecular events and compensatory processes, thus providing valuable data on the efficacy and safety of the tested drugs [71, 72]. One of the future directions for personalized medicine is that a potential therapy might be tested first in iPSCs from a HD patient to determine its efficacy and safety. If the therapy becomes approved, the same approach could be adopted to determine the diseased individuals suitable for this therapy, thereby averting potential adverse effects in patients who do not benefit from it [53, 73].

Pluripotent Stem Cells for Cell Replacement Therapy

As HD advances, a late-stage intervention might be replenishment of lost neurons by cell replacement therapy, thus reversing disease phenotypes and slowing the progression of neurodegeneration [74, 75]. Early pioneer clinical studies transplanted fetal striatal tissues into the striatum of HD patients, providing evidence that the allografts led to short-term motor and cognitive improvements [76–78]. Intractable issues associated with fetal grafts include their limited source and prolonged immunosuppression, along with the controversial ethical concerns [79]. Recently, an increasing interest is focused on alternative approaches of using pluripotent stem cells as a more favorable source to replace dying or damaged neurons

in neurodegenerative disorders [14]. ESCs or iPSCs are able to differentiate into the target cell types affected in disease and provide a readily obtainable source of graft material. Furthermore, iPSCs have the ability to generate patient-specific neural precursors, thus eliminating possible problems of immunological rejection. However, the HD-iPSC-derived cells still carry the causative mutation which would produce toxic mutant proteins and lead to ultimate cell death. Of note, emerging gene therapies such as RNAi, ASOs, and genome-editing approaches are capable of silencing or repairing the *mHTT* gene [44]. Therefore, transplantation of the corrected neural cells back into the patient brain would then abate immune rejection, replenish lost cells, and rescue functional deficiencies [56, 75].

Nowadays, pluripotent stem cell transplantation in the context of HD is largely carried out in preclinical animal models of HD (Table 2). A few human ESC/iPSC transplantations in rodent HD models have shown success in substituting for damaged neural cells [80–82]. Aubry et al. first directed human ESCs into neural, neuronal, and striatal differentiation in vitro before transplantation, and then observed that the grafted striatal progenitors successfully differentiated into mature GABAergic neurons in vivo [80]. Another study by Ma et al. also demonstrated the ability of human ESCs to differentiate into DARPP-32^{+} GABAergic cells [81]. Furthermore, transplantation of these GABAergic neurons and their progenitors into the striatum of chemical-lesioned mice led to the generation of large populations of mature GABAergic neurons [81]. These human GABA neurons were found to integrate with host neurons and correct locomotion deficits of HD mice, further substantiating the therapeutic potential of human ESC-derived cells [81]. Delli Carri et al. employed a new differentiation protocol which simulated the normal neurodevelopment of the ventral telencephalon to induce both human ESCs and iPSCs to give rise to NPCs [82]. In addition, they differentiated NPCs into GABAergic neurons which not just expressed typical MSN neuronal markers but also carried dopamine and adenosine receptors [82]. When grafted into the striatum of chemical-lesioned rats, human pluripotent stem cell-derived NPCs successfully survived and differentiated toward a MSN fate, leading to a restoration of apomorphine-induced rotation behavior [82]. Recently, the efficacy and safety of rodent iPSC grafts have also been evaluated in HD animals. These grafted rodent stem cells were able to differentiate into DARPP-32^{+} neurons in the lesioned striatum and ameliorate the corresponding striatal atrophy [83, 84]. Transplantation of mouse iPSCs also improved recovery of learning and memory deficits induced by quinolinic acid [84]. Moreover, glucose metabolism of the injured striatum by microPET/CT scanning was enhanced at 4–6 weeks post-transplantation [84]. It is noteworthy that these positive benefits are mostly present in lesioned rodent models of HD, which are far from accurately modeling the disease's main pathological features. Actually, in the past few years, we have seen many failures in clinical trials on potential therapies that showed efficacy in animal studies of HD [50]. In view of the limitations of the animal models used, preclinical data need to be rigorously and objectively assessed before translation into clinically relevant therapies.

Although iPSCs have the ability to differentiate into the desired neuron types, recent evidence suggests that the functional benefits of stem cell therapies may be mediated by secretory molecules in addition to cell replenishment. Many types of stem cells produce a variety of growth factors, cytokines, and chemokines in an autocrine/paracrine manner, playing important roles in neuronal survival, neurogenesis, and mitochondrial activation

[85]. A number of investigators have further examined the potential benefits of genetically engineered stem cells that could overexpress trophic factors like BDNF and glial-derived neurotrophic factor [86]. Recently, a group transformed iPSCs into NPCs engineered to overexpress BDNF. Importantly, intracerebroventricular transplantation of these neural cells reversed the immune impact caused by lipopolysaccharide and blunted the stressor-induced corticosterone response [87]. This combination of iPSCs and trophic factors overexpression could potentially stimulate neurogenesis and repair, and contribute to neuroprotection, thus offering great potential in disease-modifying treatment of HD.

However, the therapeutic promise of cell replacement therapy in HD is debatable. During the long-term follow-up of HD patients treated with fetal striatal grafts, functional benefits in transplanted patients have not been robust or sustainable, and some cases even showed progressive deterioration over time [88, 89]. Cicchetti et al. reported that neural transplants in HD patients underwent disease-like neuronal degeneration with a preferential loss of striatal projection neurons [90]. Furthermore, the group described the presence of $mHtt^{+}$ aggregates in striatal fetal allografts in HD patients following transplantation [25]. Jeon et al. studied the in vivo effects of HD patient-derived iPSCs following transplantation in either chemical-lesioned rats or transgenic HD mice [66, 91]. Interestingly, the grafted HD-iPSC-derived neural precursors generated GABA neurons efficiently, and no $mHtt^{+}$ aggregates were detected at 12 weeks post-transplantation [66, 91]. However, when the grafted cells were analyzed at 33 weeks, there were clear signs of HD pathology [66]. In recent years, there have been accumulating in vitro evidences for cell-to-cell transfer of mHtt oligomers/aggregates [92–95]. Most recently, Pecho-Vrieseling et al. reported transneuronal propagation of mHtt protein pathology in the corticostriatal pathway, which is early and severely affected in the HD brain [96]. Surprisingly, another study observed that neuronal Htt aggregates were able to access and initiate a prion-like conversion of normally soluble, cytoplasmic Htt in the glia of the *Drosophila* brain [97]. These findings raise uncertainty about cell replacement therapy for the treatment of HD. There remains much debate as to the exploration of cell replacement therapy as a therapeutic strategy for HD.

Conclusion and Future Perspective

Although still in its infancy, the tremendous potential of iPSC technology opens up exciting new opportunities for investigation of neurodegenerative disorders. As iPSCs are generated directly from affected patients, they are likely to represent the most genetically and molecularly accurate model of the disease. Therefore, using iPSC lines for disease modeling may bridge the gaps between animal models and human neural cells, helping elucidate the molecular basis of HD. Furthermore, iPSC technology could be coupled with high-throughput screening that provides a faster and more efficacious platform to assess a number of former and novel drug candidates aimed at stopping or slowing disease process. However, many tasks remain to be fulfilled to enable iPSC technologies to accurately model HD and to develop new therapeutics. It is unclear what the readout can be for the screening in the case of HD because the spontaneous formation of $mHtt^{+}$ aggregates has not been detected in iPSC-derived cells from HD patients. Thus, the next step will necessarily involve developing an accurate assay system for disease-associated phenotypes. For future research involving iPSC-based systems to model disease, it may be beneficial to focus on molecular changes in

HD-iPSCs that occur in patients prior to cell death or the onset of symptoms. Unraveling such reversible phenotypes in iPSCs that appear early in the course of HD, for example, alterations in gene transcription, and adapting these cells for drug development assays may be key to finding pharmacological interventions that can prevent neurodegeneration long before the devastating late-stage consequences occur.

iPSCs not only are invaluable tools for disease modeling and drug discovery in HD but also have emerged with great potential in areas of cell replacement therapy. Further gene-silencing technologies based on patient-specific iPSCs may offer an opportunity to correct this monogenic disorder, paving the way for personalized medicine. Although promising, successful implementation of iPSC-based therapy is far from becoming a reality. Nowadays, pluripotent stem cell transplantation in the context of HD is largely carried out in rodent models, and there are still enormous hurdles to be overcome as the field moves forward. Replacing complete neural circuits in the adult brain is clearly challenging. Although several studies in rodents indicate the differentiation of ESC/iPSCs into neurons with MSN properties, detailed mechanisms by which the transplanted cells differentiate into the correct cell type and integrate with host cells remain to be clarified. Most notably, mHtt protein is expressed in all cells of the brain and indeed of the body of patients. Even though striatal transplants were initially effective at early stages, this efficacy would not be sustained once mHtt induced neurodegeneration of the cerebral cortex and other brain regions. Recently, accumulating evidence for cell-to-cell transfer of mHtt raises uncertainty about cell transplantation for the treatment of HD. Therefore, further thoughtful and rigorous attempts are needed before translation of preclinical transplant results into clinic.

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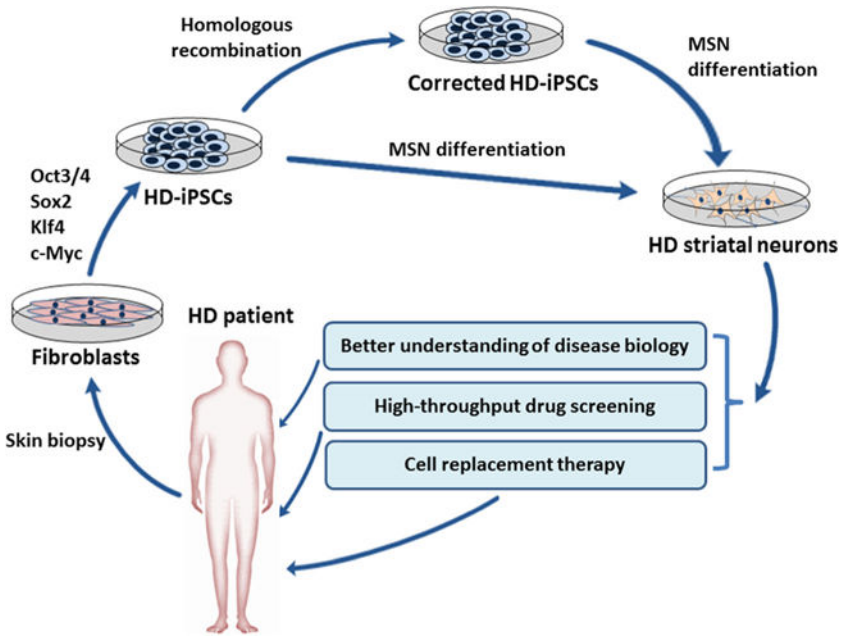

Fig. 1.

The generation and application of iPSCs in HD research. HD patient-specific iPSCs can be obtained by reprogramming of skin fibroblasts. Established iPSCs can be used as a tool for better understanding the molecular basis of HD. iPSC technology can also be coupled with high-throughput screening that provides a more efficacious platform to assess novel drug candidates aimed at stopping or slowing disease process. Moreover, HD-iPSCs can be differentiated into specific cell types predominantly affected in the disease (striatal MSNs). Emerging gene therapies make the genetic correction of HD-iPSCs become feasible, paving the way for autologous transplantation strategies of healthy iPSCs or iPSC-derived neural cells

Table 1

Human iPSC-based models of Huntington's disease

Donor cell	*HTT* mutation	Phenotype in iPSCs and/or generated neural cells	Reference
HD patient fibroblast	72 CAG repeats	No apparent difference from control iPSCs	[57]
HD patient fibroblast	72 CAG repeats	Enhanced caspase-3/7 activity upon growth factor deprivation in HD-iPSC-derived NSCs	[58]
HD patient fibroblast	72 CAG repeats	Increased caspase-3/7 activity, mitochondrial dysfunction, and decreased BDNF transcription upon growth factor removal in HD-iPSC-derived NSCs	[55]
HD patient fibroblast	72 CAG repeats	Differentially expressed protein patterns in proteomic analysis, upregulated oxidative stress-related proteins and downregulated cytoskeleton-associated proteins, more DNA damage-mediated apoptosis, reduced neuronal differentiation efficiency and neurite length	[59]
HD patient fibroblast	71 and 109 CAG repeats	Dysregulation of the MAPK-ERK signaling pathway, altered expression of oxidative stress-related proteins and p53 in undifferentiated pluripotent HD-iPSCs	[60]
HD patient fibroblast	2 homozygous genotypes (between 39 and 44 CAG repeats) and 1 heterozygous genotype (45 CAG repeats)	No differences in reprogramming, growth rate, caspase activation, or neuronal differentiation; increased lysosomal activity in HD-iPSCs and derived neurons	[61]
HD patient fibroblast	180, 109, and 60 CAG repeats	Transcriptional changes involved in signaling, cell cycle, axonal guidance, and neuronal development; changes in the actin cytoskeleton; decreased cell-cell adhesion; impaired energy metabolism; altered electrophysiological properties; increased susceptibility to cell stressors such as BDNF withdrawal and glutamate	[62]
HD patient fibroblast	109 and 50 CAG repeats	Elevated cytoplasmic vacuolation which increased over time in HD-iPSCs derived astrocytes	[64]
HD patient fibroblast	72 CAG repeats	mHtt aggregate formation upon proteasome inhibition or at later stages of transplantation into rat brains	[66]
HD patient fibroblast	180, 109, and 60 CAG repeats	Contained more neural progenitor cells after differentiation, enhanced vulnerability to BDNF withdrawal in the juvenile-onset HD lines	[63]

Table 2

Pluripotent stem cell transplantation in preclinical animal models of Huntington's disease

Species of grafted material	Stem cell class	Concentration of grafted cells	Animal model	Outcome	How long post-transplantation outcomes were observed	Reference
Human	ESC	25,000–100,000 cells/μl	Quinolinic acid-lesioned adult OFA and nude rats, weight 220–260 g	Differentiated into mature GABAergic MSNs in vivo	13–21 weeks	[80]
Human	ESC	50,000 cells/μl	Quinolinic acid-lesioned adult male SCID mice, 10 weeks of age	Generated large populations of DARPP-32$^+$ GABA neurons which made connections with host neurons, corrected the motor deficits	4, 8, 12, 16 weeks	[81]
Human	ESC/iPSC	250,000 cells/μl	Quinolinic acid-lesioned female Lister hooded rats	Differentiated into DARPP-32$^+$ neurons, restored apomorphine-induced rotation behavior	3, 6, and 9 weeks	[82]
Sprague Dawley rat	iPSC	200,000 cells/μl	3-Nitropropionic acid-lesioned male and female Sprague Dawley rats, 7.5–8.5 weeks of age	Differentiated into DARPP-32$^+$ neurons; preserved motor function; reversed histological changes including striatum atrophy, lateral ventricle enlargement, and an increase in striosome size	4–10 weeks	[83]
C57BL/6 mouse	iPSC	50,000 cells/μl	Quinolinic acid-lesioned adult male Sprague Dawley rats, weight 250–280 g	Survived and migrated into the lesioned striatum, differentiated into neurons and astrocytes, enhanced glucose metabolism, improved learning and memory function as well as striatal atrophy	1, 2, 4, and 6 weeks	[84]