Chapter 5

Cell Therapy in Huntington's Disease

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Additional information is available at the end of the chapter

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Abstract

Huntington's disease (HD) is a rare neurodegenerative disease inherited in an autosomal dominant pattern. Expanded cytosine-adenine-guanine (CAG) repeats (polyQ) in the huntingtin gene cause the aggregates of abnormally expanded polyQ-containing huntingtin protein, and striatal medium spiny neurons are shown to be the most vulnerable. Affected patients develop cognitive, motor, and psychiatric symptoms typically in middle age, and several pharmacological drugs are currently used for symptomatic relief. Since the effect of current therapies is very limited and there is no way to modify disease progression, there is an unmet need for developing new therapies for HD. Toxin or genetic rodent models are widely used for drug development, and large animal models are also available. Previous studies transplanting cells originating from embryonic or fetal striatal tissues, neural stem cells, mesenchymal stem cells, and induced pluripotent stem cells (iPSCs) in HD animal models have shown the possibilities of clinical trials. Because clinical trials performed using human fetal striatal cells have shown variable outcomes, future directions of cell therapy in HD should consider the reconstitution of a functional dynamic information-processing circuit without ectopic connections. Another major challenge is to achieve controlled differentiation of embryonic stem cells or iPSCs into specific neuronal phenotypes.

Keywords: Huntington's disease, Animal models, Stem cells, Cell therapy, Transplantation

1. Introduction

Huntington's disease (HD) is an inherited neurodegenerative disease caused by expanded CAG repeats in the huntingtin gene (*Htt*) on chromosome 4, which give rise to the formation of aggregates of mutant huntingtin proteins. Affected patients gradually develop cognitive decline, motor dysfunction (i.e., chorea or bradykinesia), and psychiatric disturbance that lead to progressive disability and death within approximately 15–20 years of disease onset. Since Huntington's disease is inherited in an autosomal dominant manner (i.e., 50 % of children are at risk) and the symptom onset occurs typically in middle age (median age, 35–40 years), affected patients and their family members suffer from significant economical and psychological burdens. Unfortunately, current therapies only target symptomatic reliefs and their effects are very limited, so the need for developing new therapies for HD is in high demand.

It is important to rescue these vulnerable medium spiny neurons (MSNs) by slowing the inexorable loss of striatal neurons and to delay the loss of striatal volume in affected patients, in view of HD pathology where striatal MSNs are shown to be most affected. More recently, stem cell strategy has been proposed to restore GABAergic striatal projection neurons into the putamen and the caudate, thereby reestablishing the degenerating striatopallidal circuit. According to previous research, transplanted cells originating from embryonic or fetal striatal tissues in HD animal models are connected with appropriate targets in the host brain and function both electrophysiologically and neurochemically to certain extents. Although clinical trials based on these preclinical studies have been performed using human fetal striatal cells, they have shown variable outcomes: some describe no benefit while others have indicated some clinical improvements with reduced motor dysfunction or slowed disease progression. However, because the use of human fetal tissues raise ethical issues and their genetic dissimilarity to the recipient is associated with the risk of immune rejection, other suitable non-fetal cell sources of syngeneic donor tissue would be advantageous. Recently, although induced pluripotent stem cells (iPSCs) generated from skin fibroblasts of HD patients have been demonstrated as an alternative autologous cell source, these HD patient-derived iPSCs carry genetic mutations, meaning that they have to be corrected to normal genes in order to be used for cell therapy. For clinical applications, it will be essential to use transgene-free reprogrammed iPSCs that are derived from patients under good manufacturing protocol (GMP) conditions. In addition to this iPSC approach, it may be worthwhile to consider using mesenchymal stem cells (MSCs), which are widely used in clinical trials, for the treatment of HD.

In this review, we describe the characteristics and limitations of current therapeutics and the need for developing novel ones. Then, animal models commonly used in HD research, various cell sources for transplantation, and the results and problems of preclinical and clinical studies so far are also discussed. Finally, we discuss the future directions of HD research and the clinical applications of stem cells. By doing so, we aim that the readers can acquire a thorough knowledge of HD and an understanding of the need for and the current view of cell therapy in HD.

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2. Characteristics of Huntington's Disease

Huntington's disease (HD) is a progressively deteriorating neurodegenerative disorder caused by expanded polyglutamines (polyQs) with more than 35 CAG repeats in the huntingtin gene (*Htt*) on chromosome 4. Htt protein is approximately 350 kDa and is composed of ten HEAT (**h**untingtin, **e**longation factor 3, protein phosphatase 2**A**, and the yeast P13-kinase **T**OR1) repeats, which form α-helical structures participating in intracellular transport [1]. Htt protein is a ubiquitously expressed soluble protein [2]. Cytosolic Htt has been shown to bind microtubules and vesicles [3], whereas up to 5 % of Htt protein has been shown to locate within the nucleus [4]. Htt protein is known for its involvement in microtubule-mediated vesicle transport, endocytosis, secretory process, and regulation of gene transcription/RNA trafficking, in line with its location within the cell [5].

Interference with transcriptional regulation (e.g. CREB)
Decline of neurotransmitter receptors and brain-derived neurotrophic factor (BDNF) level
Interference with chaperone, proteasome (UPS), and autophagy activities
Disrupted axonal transport and synaptic transmission; cytoplasmic sequestration of transcription factors
Mitochondrial (complex I/II) dysfunction: calcium dysregulation/defective energy metabolism
Excitotoxicity via NMDA glutamate receptors
Activation of microglia and macrophages
Increased Kynurenine 3-monooxygenase (KMO) and 3-hydroxykynureine production: oxidative stress
Apoptosis/Necrosis

Table 1. Pathologic mechanisms of Huntington's disease

It is still under debate whether the effect of mutant Htt protein is through a "gain-of-toxic function" or a "loss of function," and various mechanisms have been suggested to elucidate the pathologic mechanisms of HD (Table 1). For example, mutant Htt that is translocated into the nucleus can interfere with gene transcription via either direct binding to DNA or interacting with several mediators including CBP (cAMP response element binding protein), NCoR (nuclear receptor corepressor), SP1 transcription factor, basal transcription factors, and REST (repressor element 1 silencing transcription factor) element [6, 7]. This reduced transcription can decrease the level of brain-derived neurotrophic factor (BDNF) in the brain of HD patients. Other loss-of-function mechanisms of Htt for disease pathogenesis have also been proposed [8, 9]. It is worth noting that Htt is necessary for early embryonic development and *Htt*-null mice demonstrate increased apoptosis [10]. A "gain-of-toxic-function" is another important mechanism of toxicity of mutant Htt. For instance, because a highly expanded *Htt* gene in HD leads to an Htt protein containing an abnormally expanded polyQ segment, toxic N-terminal fragments of abnormal ß-sheets are formed [11]. Other posttranslational factors also promote toxicity of mutant Htt, such as conformational change, aggregation propensity, cellular localization, and clearance rate. Mutant Htt binds to mitochondria and alters mitochondrial metabolism, which may result in energy defects, oxidative stress, and disturbed calcium

homeostasis [12]. Moreover, protein clearance systems are shown to be impaired in HD patients and in models [13]. Irrespective of the mode of patho-mechanism, Htt aggregates within the cytoplasm and the nucleus, and selective neuronal cell loss and atrophy occur predominantly in the striatum and the neocortex [14]. Altogether, HD develops mainly through a "gain-of-toxic-function" mechanism from an abnormal conformation of mutant Htt [15, 16].

HD is an inheritable disease passed down in an autosomal dominant manner. The prevalence of HD is 4–10 per 100,000 in Western countries and approximately 0.4 per 100,000 in Asian countries [17]. Disease onset is typically in middle age (median age, 35–40 years), but it can also occur less commonly in juveniles and in old age depending on the CAG repeat number and/or modifying genes and environmental factors [18]. The studies on the relationship between CAG repeat number and disease manifestation demonstrated that there is an inverse correlation between age at initial symptom onset and the length of the expanded CAG repeat [19], and the correlation determines the age of onset with approximately 50–60 % variation [20, 21]. During HD, the disruption of the corticostriatal pathway, the main pathway affected, causes progressive cognitive decline, motor dysfunction, psychiatric disturbance, and ultimately death within approximately 15–20 years [22]. Although CNS degeneration attributes to these core symptoms, widespread pathology throughout the body may also contribute to other general symptoms such as weight loss, skeletal muscle wasting, metabolic and endocrine dysfunction, and dysfunction of cells of the hematopoietic lineage [13, 23].

Large aggregates of abnormally expanded polyQ-containing Htt protein, which form intranuclear inclusion bodies, are the pathological signatures of HD. Although the aggregates of mutant Htt are widespread throughout the brain and body, the striatum-selective damage encompassing the loss of striatal volume and up to 95 % loss of GABAergic medium spiny neurons (MSNs) is seen in the corticostriatal pathway [24]. This striatal selectivity might be explained by a possible involvement of a Ras homolog enriched in striatum (Rhes), a striatal-specific protein that binds to mutant Htt and increases the cytotoxicity of Htt through SUMOylation in HD pathogenesis [25]. Other than SUMOylation by Rhes, posttranslational modifications generally on the N-terminal 17 amino acids of Htt, including phosphorylation, ubiquitination, palmitoylation, and SUMOylation of huntingtin-associated (interacting) proteins, have important roles in modulating the toxicity of Htt as well as the selective neuronal loss [26]. Among the posttranslational modifications, phosphorylation has been shown as the major process for modulating Htt. Phosphorylation at serines 13 and 16 of Htt has been demonstrated to be protective against motor and psychiatric dysfunction and neuropathology [27]. Palmitoylation of Htt at cystein 214 has been shown to enhance its membrane association, whereas an expanded Htt shows less palmitoylation and an associated increase in neuronal toxicity [28]. Small ubiquitin-like modifiers (SUMO) are proteins that covalently attach to and detach from the target protein to modify their function, a process described as SUMOylation. Several SUMO proteins are known to interact with Htt-related proteins (huntingtin-associated protein 1 (HAP1) and transcription elongation regulator 1) [13], and SUMOylation of these proteins by SUMO may be related to the pathogenesis of HD. Lastly, a disruption of BDNF

support or an increased susceptibility to glutamatergic excitotoxicity of the neuronal circuit between the cerebral cortex and the striatum can lead to HD pathogenesis [29].

In HD pathogenesis, selective striatal neuronal loss comes not only from cell-autonomous toxicity but also cell-cell interactions. Cell-cell interactions occur between both interneuronal connections and between glial cells and neurons. In interneuronal connections, mutant Htt causes increased stimulation of extrasynaptic glutamate receptors and a decreased reuptake of glutamate by glia, leading to enhanced excitotoxicity and metabolic toxicity. Neuron and glia coculture experiments showed that expressing mutant Htt in glia triggered neuronal death only in cells expressing mutant Htt, providing evidence for the role of mutant Htt in neuronal excitotoxicity [30]. Further, HD patient-derived astrocytes alone were shown to replicate HD pathology when Htt with expanded CAG repeats was expressed [31]. Similarly, in astrocytes, transgenic expression of mutant Htt alone led to HD-like symptoms or worsened disease progression when crossed into existing HD models or even into normal mice [32]. In HD patients, microglia are activated in prodromal stages, and then symptoms manifest in HD. The level of microglial activation has been shown to correlate with disease severity and striatal loss *in vivo* [33, 34].

3. Current therapeutics in clinical practice and its limitation: Need for developing novel therapeutics

Several pharmacological drugs are currently used for symptomatic relief of HD symptoms such as hyperkinetic involuntary movements and mood disorders, and there is no way to modify disease progression. For hyperkinetic involuntary movements including chorea, myoclonus, and dystonia, dopamine-depleting agents (tetrabenazine), antipsychotics (haloperidol, pimozide, clozapine, olanzapine, ziprasidone, aripiprazole, risperidone, and quetiapine), benzodiazepines (clonazepam), anticonvulsants (sodium valproate and levetiracetam), and botulinum toxin can be prescribed. Because tetrabenazine is not only a dopamine-depleting agent but may also decrease brain serotonin and norepinephrine concentrations, it potentially causes or aggravates depression [35]. Various neuroleptics (olanzapine, quetiapine, risperidone, sulpiride, haloperidol, and clozapine) that are also used for psychiatric symptoms should be administered with caution because they may induce tardive dyskinesia and other adverse effects. Clozapine is well known for being costly and inducing irreversible agranulocytosis. For mood disorders, antidepressants (citalopram, fluoxetine, paroxetine, sertraline, mirtazapine, and venlafaxine) and anxiolytics (benzodiazepines, propranolol, and clonidine) are used [13]. A range of psychiatric drugs can alleviate some of the more overt disturbances of mood and hyperactivity in HD; however, these drugs have limited effects and are associated with side effects [36]. There is limited evidence in the literature for the use of acetylcholinesterase inhibitor (rivastigmine and donepezil) for cognitive dysfunction in HD [36, 37].

Behavioral and social interventions are often as effective as drug therapy for behavioral difficulties. For instance, weight loss frequently leads to general weakening [38] and a higher

body mass index has been associated with a slower rate of disease progression [39], meaning that adequate nutrition may be another important aspect of therapy. Other than nutrition, environmental enrichment and physical, speech, and occupational therapy are also usually recommended to delay the onset of HD, some of which have been validated in mouse models [40, 41].

HD is one of few neurodegenerative diseases for which the diagnosis can be made long before the onset of clinical symptoms by predictive genetic testing. This offers an opportunity to intervene in the earliest stages of neurodegeneration and thereby slow down or arrest disease progression. Many drugs targeting various mechanisms underlying HD pathogenesis have been tested. However, antiexcitotoxic drugs, such as riluzole (an antiglutamatergic drug) [42], vitamin E [43], idebenone and remacemide (an NMDA ion channel blocker) [44], minocycline (a caspase-3 inhibitor and anti-inflammatory agent) [45], and creatine (energy metabolites, CREST-E trial) [46] have failed in clinical trials so far. More favorable results from animal studies using memantine (an NMDA receptor antagonist), coenzyme Q10 (a mitochondrial cofactor and an antioxidant), and ethyl eicosapentaenoate (an antioxidant) have been highlighted, but none of these compounds was successful. Currently, reducing the expression of mutant Htt protein with RNA interference or antisense oligonucleotides is the most promising candidate and other approaches of various mechanisms are being designed and under investigation [47].

4. Animal models of Huntington's Disease

4.1. Rodent models in Huntington's Disease

Rodent models have played an important role in providing experimentally accessible systems to study various clinicopathological findings and pathogenesis of HD and to test potential therapeutics of their efficacy [48]. From the late 1970s, several investigations started to generate animal models of HD. Glutamate-related excitotoxin kainic acid (KA) and quinolinic acid (QA) were used to induce the degeneration of striatal GABAergic projection neurons while preserving striatal afferents, thereby producing a model that resembles the neuropathologic condition in HD [49, 50]. Because of marked epileptogenic side effects in KA model, QA model is favored and currently used. Another toxic model of HD is made by producing defective energy metabolism through toxins such as sodium azide, malonate, and 3-nitropropionic acid (3-NP). For example, 3-NP-induced inhibition of mitochondrial complex II effectively produces striatal lesions that were similar to the cell loss in HD [51, 52]. To mimic the chronic progressive nature of human HD, chronic administration of metabolic toxin has been tried in experimental primates; however, higher inter-animal variability and nonspecific striatal damage in primates (NO replacement; just delete please) limit this approach [53]. Altogether, despite their usefulness as mimics of striatal pathology and behavioral manifestations of HD, toxin models were limited because it was not possible to study disease progression or to replicate the widespread neuropathology observed in the human condition [54].

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After the discovery of the HD gene in 1993, genetic models of HD have been generated, and over 20 different rodent models have been generated to date [55]. Genetic models provide accurate and experimentally accessible systems in which to study the molecular pathogenesis. Moreover, they provide an opportunity to test the effect/efficacy of candidate therapeutics and explore their potential for clinical applications. Because the degree of overexpression of mutant Htt protein plays a significant role in the phenotype in mice, genetic mouse lines have been generated with varying degrees of phenotype by incorporating variations of mutant huntingtin gene into the mouse genome. The mouse models fall into three categories (Table 2): (i) mice that express truncated N-terminal fragment (exon-1 or exons 1 and 2) of the human *Htt* gene containing polyglutamine mutations [56-60]; (ii) mice that express the full-length human HD gene [61-65]; and (iii) mice with pathogenic human CAG repeats inserted into the existing CAG expansion in murine *Htt* (knock-in models) [66-70]. Although all of these models develop the typical findings of human HD, the degree and the progression to which the behavioral features and pathological findings manifest differ, as well as the developmental speeds. Among them, the R6/2 mice showed the most prominent motor, behavioral, and cognitive phenotypes as well as marked weight loss and death by 13~15 weeks of age. In this strain, various mechanisms of HD pathogenesis are demonstrated, including the intraneuronal nuclear inclusions; impaired mitochondrial function [71]; abnormalities of glutamatergic, dopaminergic, and cholinergic receptors in the striatum [72]; and abnormalities in synaptic plasticity in the hippocampus [73, 74]. The full-length *Htt* gene (transgene) is incorporated into the mouse genome via bacterial artificial chromosome (BAC) or yeast artificial chromosome (YAC). Meanwhile, the phenotypes in the full-length *Htt* mutation model develop gradually over several months and may survive as long as the wild-type animal [75]. This model is especially valuable for studies on the proteolytic mechanism of full-length *Htt*, its clearance, and the evaluation of the presymptomatic stages of HD. Among the full-length HD genetic models, the YAC mouse model with 128 CAG repeats (YAC128) develops motor abnormalities, composing of an initial hyperactivity and followed by difficulty in motor control from six to 12 months and then hypokinesia [76]. Further, other motor dysfunctions, including circling behavior, hind limb clasping, and gait abnormalities, may be seen as early as three months [77]. Although the full-length models are genetically more accurate, the fragment *Htt* models have been used more frequently for their aggressive phenotype, rapidly progressive disease course, well-defined behavioral and pathological findings, and early death. Moreover, due to the prolonged disease progression in the full-length *Htt* models, it is hardly possible to use progressive morbidity and survival as endpoints [53].

While toxin models play a role in understanding mechanisms of excitotoxicity and mitochondrial dysfunction in HD, they cannot replicate the progressive neurodegenerative course characterized by the misfolding of the mutant Htt protein in HD. Alternatively, genetic animal models provide a good platform to explore the progressive manifestation of neuropathology and cognitive, behavioral, and motor dysfunction [48]. It also provides the platform to test potential therapeutics for future translational research. However, standardization of sample size, inclusion/exclusion criteria of mice, and the onset and duration of treatment, as well as the outcome measurement of preclinical trials, are critical to compare the effectiveness of candidate therapeutics [78].

Model	CAG-N	Behavioral changes	Neuropathology	Survival
Transgenic models: Truncated N-terminal fragment				
R6/1, Mouse [56, 57]	116	Decreased anxiety Significant weight loss Abnormal motor performance	Reduced brain volume Loss of striatal neurons Htt aggregates Reduced dopamine levels	12+ months
R6/2, Mouse [58]	144–150	Dystonia with limb clasping Significant weight loss Reduced motor performance Seizures, Diabetes	Gross brain atrophy Progressive neuronal atrophy with neuronal loss Htt aggregates Astrogliosis Reduced dopamine levels	12–18 weeks
N171-82Q, Mouse [59]	82	Weight loss Abnormal motor performance Limb clasping Visuospatial memory loss	Gross brain atrophy Atrophy and loss of striatal neuron Htt aggregates	130–180 days
HD51, Rat [60]	51	Significant weight loss Deficient motor performance Reduced anxiety Cognitive deficits Head dyskinesias	Enlarged ventricles Striatal neuronal loss Htt inclusion	NA
Transgenic mouse models: Full-length human *Htt*				
YAC 128 [62, 76]	128	Hyperactivity (initial); hypokinesia (later) Abnormal circling behavior Hindlimb clasping Deficient motor performance Gait abnormalities	Decreased striatal and cortical volume Reduced striatal neuron area and number Progressive Htt aggregates	Slightly decreased
BACHD [64, 78]	97 (Mixed CAA/CAG repeat)	Significant reduction in motor function (2 months) Behavioral worsening (12 months)	Marked gross brain atrophy and brain weight loss Significant cortical and striatal volume loss (12 months) Degenerating neurons in striatum (12 months) Htt inclusions in entire cortex; a few small inclusions in striatum	Normal lifespan
Hu97/18 [65]	97	Motor learning deficit (2 months) Deficits in both spatial learning and object recognition (9 months) Increased stereotypy or repetitive movement Anxious and depressive-like behaviors	Forebrain atrophy Striatal volume loss Cortical shrinkage and white matter loss (12 months)	NA

Model	CAG-N	Behavioral changes	Neuropathology	Survival
Knock-in mouse models: Full-length *Htt*				
HdhQ111 [66, 68]	111	Gait impairment (13 months)	Diffuse Htt activity (6 weeks) with nuclear inclusions (12 months) Astrogliosis (24 months)	Normal life span
CAG140 [69]	140	Body weight loss Hyperactivity (initial); hypoactivity (later) Gait abnormalities (12 months)	Nuclear and neuropil aggregates (8 months) Diffuse Htt (2 months) Neuronal loss	Normal life span
CAG150 [70]	150	Body weight loss (70 weeks) Motor performance deficits on rotarod, gait, and beam balance (70–100 weeks)	Striatal Htt aggregates (28 weeks) Nuclear inclusions (37 weeks) Reactive astrogliosis (56 weeks) Loss of striatal neuron perikarya and volume (100 weeks in homozygous mice)	Normal life span

Htt=huntingtin protein; NA=not available

Table 2. Rodent models of Huntington's disease

4.2. Large animal models in Huntington's Disease

Nonhuman primates are genetically more similar and have a more similar physiology to humans than rodents, making them invaluable for modeling human disorders and for developing therapeutic strategies. Nevertheless, only a limited number of works has been reported in HD. The use of nonhuman primates is focused on the study of HD-like behavioral manifestations, especially for chorea, and the development of potential therapeutics for HD. In the case of nonhuman primate study, the toxin models using QA or 3-NP were most commonly used [52, 79]. After the development of transgenic nonhuman primate models of HD in 2008, the potentials of using large animals in HD research have been spotlighted. There are three types of large animal models: a rhesus monkey (Macaca mulatta) [80], a miniature pig model [81], and a sheep model (Ovis aries) [82]. The rhesus macaque and pig models were generated using fragments of human mutant *Htt* and the sheep model using the full-length human coding sequence of *Htt*. By injecting oocytes with lentiviruses expressing exon1 of *Htt* carrying 84 CAG repeats, three transgenic monkeys were made, which survived for more than two years and showed clinical features of HD, including dystonia and chorea [80]. Transcriptomic dysregulation was recently reported from peripheral blood samples, which is under further clinical investigations [83]. The transgenic HD sheep model demonstrated a decreased expression of DARPP-32 (dopamine- and cAMP-regulated phosphoprotein of 32 kDa) at seven months of age and a characteristic inclusion pathology in the brain at 18 months [84].On the contrary, there were no aggregates in the brain even up to 16 months of age and no development of motor abnormalities in transgenic minipigs [85]. Because transgenic large animal models have many advantages to understand the biology of HD and the development of potential therapies, practical and ethical issues as well as preclinical works should be also considered.

5. Source of cell therapy for striatal transplantation in HD

A characteristic pathological feature in Huntington's disease is a selective loss of medium spiny projection neurons (MSN) in the striatum. Thus, cell therapy in HD is aimed at replacing the MSN and making them functionally active by connecting them to the host neuronal network [86]. To accomplish this, transplanted cells should survive, differentiate in vivo into the proper cell type (i.e., MSN), be functionally active, and connect with appropriate target neurons, thereby reestablishing the degenerating striatopallidal circuit [87, 88]. A number of potential stem/progenitor cells have been studied that include embryonic stem cells; multipotent progenitor cells from the embryo or fetus, which are already partially committed to a neural lineage; cells from the umbilical blood; autologous or allogenic adult stem cells from various tissues; and finally induced pluripotent stem cells [53]. The majority of cells used so far are fetal neural stem/progenitor cells, but adult stem cells or iPSCs can be alternative cell sources to fetal or embryo-derived stem cells. Before starting clinical trials, each cell type should be shown to have efficacy and long-term safety in properly designed animal models of HD.

5.1. Fetal neural stem cells and fetal neural progenitor cells

Fetal neural stem cells (NSCs) are isolated from the fetal brain at various gestational periods and from multiple brain regions [89]. After the collection of primitive cells and their short-term expansion in vitro, these cells are transplanted into the lesioned brain of an adult rodent. Majority of previous studies have used fetal neural progenitors (FNPs), which are expanded as neurospheres prior to transplantation (Table 3), and the transplanted FNPs showed evidence of differentiation into striatal-like cells [90]. Such neural differentiation depends on the characteristics of fetal neural stem/progenitor cells to respond to signals in the developing CNS [91]. For example, stem cells derived from the human fetal cortex (12 weeks post-conception) were pretreated in culture media with ciliary neurotrophic factor (CNTF) and were transplanted into QA-lesioned rats. Motor recovery and sustained striatal volume were marked and the transplanted human stem cells differentiated into neurons and astrocytes with substantial connections to endogenous cells [92]. Systemic injection of human NSC also improved neuropathologic and behavioral abnormalities [93]. Because HD showed a selective loss of MSNs in the striatum, induction of a GABAergic phenotype in immortalized striatal NSCs was tried. These GABAergic phenotype-induced cells maintained neurite processes connecting to endogenous neurons [94]. Mouse NSCs modified to secrete human nerve growth factor (NGF) were transplanted into striatal QA-lesioned rats, and it was shown that the size of lesion, the number of surviving striatal neurons, and the length of neurites were significantly improved than sham-operated rats [95]. However, despite these successes based on fetal stem/progenitors, the use of in vitro expanded fetal neural stem cells is limited because they lose the capacity to differentiate into various neural cell types and tend to go into senescence after several passages of culture [96]. Moreover, there is an intrinsic ethical issue associated with the use of aborted fetal tissue. Recently, a cloned human striatal neural stem cell line (STROC05) was transplanted in the R6/2 mouse model of HD, but the mouse model showed a disappointing suboptimal clinicopathological improvement [97] (Table 3).

Animal model	Cells	Histology	Functional outcome	Ref
Rat, QA [U]	Human stem cell-derived from fetal cortex (pretreated with CNTF)	Reduced striatal atrophy Survive and differentiate into neuron and glia Connectivity with endogenous neural cells	Improved motor performance (cylinder test)	[92]
Rat, QA [U]	Human NSC-derived from fetal human brain (systemic injection)	Reduced striatal atrophy NSC migration in and around the damaged striatum Migrated NSCs differentiated into neurons and glias	Reduced ApoM-induced rotation	[93]
Mice, QA [U] R6/2	Mouse NSC - neurosphere and dissociated cell suspension	Increased survival of graft when transplant at 2 days after lesioning	No change on BDNF expression	[94]
Rat, QA	Noggin-primed human NPC derived from human ESC	Extensive migration and large-scale differentiation Increased the extent of neuronal differentiation	NA	[102]
R6/2	undifferentiated or predifferentiated DARPP-32 cells [B] derived from human striatal neural stem cell line (STROC05)	Poor survival and neuronal differentiation both in the undifferentiated and differentiated conditions A few cells expressed the neuronal marker beta-III-tubulin.	NA	[97]
Rat, Lesions of the dorsal striatum [U]	Homotopic neural transplants (GE or cortex from E15 rat embryos of same strain)	Patches of positive DARPP-32 and tyrosine hydroxylase Significantly higher extent of DARPP-32 patches	Alleviated lateralised response deficits Prevented development of lateral disparity Restored speed of responding back to pre-lesion levels	[131]
Rat, KA	Fetal rat striatal primordia	Differentiation to spiny neuron	Restored synaptic potential	[135]
Rat, QA	Embryonic striatal grafts (Lateral GE)	Reversed lesion-induced increase in the cytochrome oxidase activity of the Gp	Reduction of ApoM-induced rotational asymmetry	[136]
Rat, Ch	Embryonic striatum	Innervated by host-derived dopamine axons	Restored response of host neurons	[137]

Animal model	Cells	Histology	Functional outcome	Ref
Rat, KA	Fetal striatal graft	NA	Restored striatal GABA overflow	[138]
Rat, IA [U]	Embryonic striatal graft	NA	Stimulation of GABA release	[139]
R6/2	Striatal grafts	Survival and differentiation of grafts	Improved general locomotor behavior No significant functional improvement	[132]
R6/1	Wild-type donor cortex	NA	No improvement	[133]
Rat, 3-NP	Human NSC (transplantation before 3-NP administration)	Reduced damage to striatal neurons Increased BDNF expression	Improved motor performance	[140]

Apo-M=apomorphin; BDNF=brain-derived neurotrophic factor; BM-MSCs=bone-marrow-derived mesenchymal stem cells; Ch= Cholecystokinin-8-sulphate; CNTF=ciliary neurotrophic factor; DARP-32=dopamine- and cAMP-regulated phosphoprotein of 32 kDa; ESC=embryonic stem cell; GABA=gamma-aminobutyric acid; GE=ganglionic eminence; Gp=globus pallidus; IA=ibotenic acid; KA=kainic acid; 3NP=3-nitropropionic acid; MSN=medium spiny neuron; NA=not available; NPC=neural precursor cell; NSC=neural stem cell; QA=Quinolinic acid; [B]=bilateral; [U]=unilateral

Table 3. Neural stem cell/progenitor cell-based treatment of HD in preclinical rodent models

5.2. Embryonic stem cell-derived neural progenitor cells

Embryonic stem cells (ESCs) are isolated and expanded from the inner cell mass of the blastocyst-stage embryo. Because ESCs are very primitive and pluripotent, they can be expanded in vitro indefinitely while retaining relatively stable cell characteristics [98]. Even after expansion, they also retain substantial neurogenic potential [99]. Their ability to expand and sustain neurogenic potential provides many advantages to be used in cell therapy; however, there have been difficulties in inducing differentiation of ES cells into striatal cells, which is especially important in HD. A report showed that mouse ES cells treated with retinoic acid could differentiate into neuronal cells that could integrate and survive in the QA-lesioned rat model of HD [100]. Another concern with the use of these cells is its potential for tumorigenicity, because even tiny numbers of undifferentiated cells at the time of transplantation may develop into tumors later on. To overcome these limitations of ES cells, research has shifted to using neural stem/precursor cells (NPCs). NPCs are a heterogeneous population of mitotically active, self-renewing, and multipotent cells, which can be isolated from the embryo [101]. Likewise, to use human neural precursors (hNP) derived from embryonic stem cells (hESCs) in HD cell therapy, hNP is required to differentiate into neuronal cells, especially MSN, in vivo. In vitro noggin priming can be an effective tool of hNP transplantation in HD treatment. Noggin-primed hNP showed survival, extensive migration, and differentiation into predominantly neuronal cells after transplantation in the QA-lesioned stratum of rats [102]. Recently, a protocol has been developed to obtain a high percentage of functional GABAergic

neurons from mouse embryonic stem cells (mESCs) [103]. By combining an in vitro culture and an in vivo differentiation protocol, striatal progenitors derived from hESCs were shown to mature into DARPP-32-positive neurons in QA-lesioned rats [104]. Using neural precursor cells with elimination of undifferentiated cells, ESC-based regenerative approaches may be successful in treating HD patients. In addition to cell replacement potential, there is evidence that transplantation of NPCs may modulate inflammatory reactions through a "bystander" mechanism [105].

5.3. Non-neural stem cells

To avoid ethical problems, non-neural stem cells, such as adult stem cells or umbilical cord-derived cells, have been used as alternative cell sources for HD treatment. Because adult stem cells are relatively easy to harvest and autologous grafting is possible, there have been many studies using mesenchymal stem cells (MSCs) of the bone marrow [106-108] or adipose tissue [109, 110] in HD mouse models (Table 4). Although there is still debate about the possibility of cell fusion events rather than true transdifferentiation, these non-neural stem cells are known to have the capacity to differentiate into neurons after injection into the adult rodent host [111]. Intrastriatal MSC transplants reduced motor and pathological deficits in a 3-NP-lesioned rat and QA-lesioned mouse/rat HD models [106, 109, 112-115]. Genetically engineered stem cells that produce trophic factors could also be a cell source for cell therapy [116-118]. When genetically engineered bone marrow-derived MSCs overexpressing neurotrophic factors (NTFs), called NTF(+) cells, were transplanted into rat brains after QA injection, NTF(+) cells survived, maintained their NTF-secreting phenotype, and exhibited improved behavior and reduced striatal atrophy associated with QA lesions [119]. MSCs engineered to produce BDNF also improved behavioral performance and reduced striatal atrophy when transplanted in YAC128 mouse model of HD [120]. In addition, MSC-based studies take advantages of the property of MSCs to modulate the brain environment toward neuroprotection [116]. Injection of cell-free extracts of adipose-derived stem cells also demonstrates behavioral and pathological improvements of R6/2 models in terms of HD pathology [121].

Animal model	Cells	Histology	Lesion volume	Functional outcome	Ref
Rat, QA	Rat BM-MSCs	Reduced striatal atrophy	Improved striatal volume	NA	[106]
Rat, QA	Human adipose MSCs	Reduced striatal atrophy and apoptosis	Decreased lesion volume	Reduced Apo-M induced rotations	[109]
Mouse, QA	Human BM -MSCs	Increased cell proliferation in striatum Reduced apoptosis	Decreased lesion volume	Improved rotarod performance Extended survival	[113]
R6/2 mouse	Human BM -MSCs	Improved cell differentiation	NA	Improved survival	[113]

Animal model	Cells	Histology	Lesion volume	Functional outcome	Ref
Rat, QA	Human BM -MSCs	Reduced striatal atrophy Increased level of NTFs	Decreased lesion volume	Reduced motor dysfunction	[114]
R6/2 mouse	Human adipose MSCs	Reduced Htt aggregates Attenuated loss of striatal neurons	Improved striatal volume	Improved rotarod Reduced clasping Improved survival	[109]
Rat, 3NP	Rat BM-MSCs	Increased striatal labeling in BDNF, collagen type-I and fibronectin	Prevented 3NP-mediated ventricle enlargement	Improved rotarod Improved paw placement	[112]
Rat, QA	Rat BM-MSCs	Improved MSC migration to lesion	Decreased lesion volume	Regenerated striatal network Reduced Apo-M induced rotations	[107]
Rat, QA	Human BM-MSCs engineered to secret NTF	Survived after 6 weeks Sustained NTF secretion	Decreased lesion volume	Reduced Apo-M induced rotations	[119]
YAC 128 mouse	Human adipose MSCs	Reduced striatal atrophy	Improved striatal volume	Improved rotarod performance/ motor function	[110]
Rat, QA	Rat BM-MSCs	NA	NA	Reduced Apo-M induced rotations Improved beam walk and hang wire time	[108]
YAC 128 mouse	BM-MSCs engineered to produce BDNF	Reduced striatal atrophy	Improved striatal volume	Improved rotarod performance Reduced hindlimb clasping	[120]
Mouse, QA	hESC-derived GABA neurons and their progenitors	Repopulated GABAergic cells, connecting with endogenous cells	NA	Improved rotarod, openfield, and tradscan performance	[142]

Apo-M=apomorphin; BDNF=brain-derived neurotrophic factor; BM-MSCs=bone-marrow-derived mesenchymal stem cells; hES=human embryonic stem cells; NA=not available; NTF=neurotrophic factor; QA=quinolinic acid; 3NP=3-nitropropionic acid

Table 4. Mesenchymal stem cell-based treatment of HD in preclinical rodent models

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5.4. Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) generated from somatic cells of patients can be used to model different human diseases, thereby enabling disease investigation and drug development [122]. Since the generation of iPSCs does not involve the destruction of human embryos, they can avoid the ethical issues related to the use of human ESCs [123]. In direct opposition to embryonic/fetal tissue-derived cells, patient-derived iPSCs can avoid immune rejection as well as ethical problems, and they can also serve as sources of transplantable cells in novel cell therapies [124]. Recently, non-integrating episomal vectors were introduced into the cell by electroporation, making transgene-free and virus-free iPSCs in a feeder-free environment [125]. There are controversial results regarding formation of mutant Htt proteins in HD patient-derived iPSCs (HD-iPSCs) [126, 127]. At least, HD-iPSCs can be differentiated into GABAergic striatal neurons and make significant behavioral recovery without aggregation formation at 12 weeks after transplantation [127]. Nevertheless, as HD is a genetic disorder, correction of HD mutations in HD-iPSCs is suggested to be an essential step before grafting to HD patients [122]. With the advent of new gene editing technologies using zinc-finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN), and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9, iPSCs that are derived from patients with gene mutations may still be a plausible cell source for transplantation [128, 129]. A nucleofection-based protocol adapted to single-cell dissociated feeder-free culture was established, and a reversal of HD phenotype and striatal differentiation of gene-corrected HD-iPSCs *in vitro* and *in vivo* are demonstrated [130]. If transgene-free reprogrammed iPSCs derived from patients could be made under good manufacturing practice (GMP), they may provide a suitable source for autologous transplantation in the future.

6. Results and problems of pre-clinical and clinical studies

6.1. Pre-clinical cell transplantation in Huntington's Disease models

In view of HD pathology, it is important to rescue the vulnerable MSNs by slowing the inexorable loss of striatal neurons. To rescue the damaged striatum, embryonic striatal tissues were transplanted, and their survival, expression of a wide range of striatal markers, and the recovery of motor and cognitive functions were demonstrated by many tasks of evaluation both in HD toxin and genetic models (Tables 3–4) [131-133]. Although the extent of functional improvement was relatively modest in transgenic animal models, it was shown that the transplanted cells can connect with appropriate targets in the host brain [134] and function both electrophysiologically [135, 136] and neurochemically [137, 138], indicating that striatal grafts can yield a functional repair of striatal cell loss in HD [139]. The timing of cell transplantation should be also considered, as the pretreatment with human NSCs was shown to rescue the motor impairment and neuronal damage caused by systemic 3-NP administration [140]. When NSCs are transplanted after excitotoxin injection, the extent of neuronal recovery could be different according to the time interval between excitotoxin injection and NSC transplantation [94]. Another consideration on the cell transplantation is that transplanted cells

should exhibit an MSN morphology, express MSN markers such as DARPP-32, and function *in vivo* to recover the lost functions [141]. Recently, hESC-derived DARPP32-expressing forebrain GABA neurons and their progenitors were implanted into QA-lesioned mice and they were connected with endogenous dopaminergic and glutamatergic neurons [142]. In the past two decades, clinical trials have been performed using human fetal striatal cells, and some reports have indicated clinical improvement with reduced motor dysfunction or slowed disease progression in some patients (Table 5). However, because human fetal tissue transplants inevitably raise ethical issues and risk of immune rejection, induced pluripotent stem cells (iPSCs) generated from skin fibroblasts of HD patients [122], can serve as an autologous cell source. HD-iPSCs could be differentiated into neural precursor cells and implantation of those cells in the striatum of QA-lesioned rats; behaviors improved significantly; and Htt aggregation was not formed at 12 weeks after transplantation [127]. In addition, various adult stem cells also demonstrated behavioral and pathological improvement after transplantations into toxin or transgenic rodent models (Table 4).

Donor tissue	N	Implant site	Safety	Efficacy	Ref
VM or WGE	4	NA [B]	No pathological or immunological response	Not possible to determine	[143]
E12-13 WGE	2	CN cavity	No surgical incidents or subsequent SEs	Slow progression	[144]
E8-9 LLGE	7	pcPu [B]	1 death from cardiac arrest, 3 subdural hematomas	Modest (NS) changes in motor tests at 12 months Transplanted cells can survive and integrate anatomically over 10 years	[146]
E9-12 WGE	4	CN + pcPu [B]	Safe; no serious SE	Stabilization or improvement in some neurological indices Prolonged graft survival with development of striatal-like structure	[148]
E7.5-9 WGE	5	2 CN + 3 Pu [B]	Safe procedure	Motor and electrophysiol improvements continue over 6 years	[145, 155]
E8-10 LGE	14	1 CN + 4 Pu [B]	Safe; no serious SEs	Benefit motor, limited neuropsychogic tests	[149, 150]
E8-12 WGE	4	2 CN + 4 Pu [U]	Only SEs related to immunosuppression	Safety only, efficacy not reported	[153]
Porcine LGE	12	2 CN + 4 Pu [U]	Safe; no serious SEs	No change on TFC over 12 months	[161]

CN = caudate nucleus; E = weeks of embryonic age; LLGE = lateral aspect of the lateral ganglionic eminence; NA=not available; NS=not significant; pcPU = postcommissural putamen; Pu = putamen; SEs = side effects; TFC=total functional capacity; WGE = whole ganglionic eminence; VM = ventral mesencephalon; [B] = bilateral implants; [U] = unilateral implants.

Table 5. Clinical trials in HD patients

6.2. Clinical trials of cell transplantation in Huntington's Disease

On the basis of the encouraging results from animal studies, clinical trials using fetal neural stem cells have been performed since 1990 (Table 5). In the early studies performed in Cuba, Czechoslovakia, and Mexico, implantation protocols and procedures were shown not to cause major complications or overt side effects [143, 144]. Afterward, extensive series of implants proved safety of the procedure in moderate stage of patients with functional and/or radiological improvement [145-148]. The first extensive series of fetal striatal tissue implantation was performed in Los Angeles, USA. The procedure was safe [149], and the results indicated motor and cognitive improvements in small numbers of patients [150]. Graft survival was identified by magnetic resonance spectroscopy [151]. Another study group in Tampa, Florida, USA, reported no overall improvement in motor function despite absence of immune rejection [146]. However, when patients with the procedure-dependent side effect (i.e., SDH) were excluded from the result analysis, motor scores were significantly improved after transplantation, and the postmortem brain analysis in one patient indicated healthy surviving grafts 18 months after transplantation and good differentiation into mature striatal-like tissue containing all striatal cell phenotypes [152]. Although three of the patients developed subdural hematoma after the surgery, this side effect could be avoided by careful selection of patients, i.e., patients without significant brain atrophy, for operation. Additional safety evaluation trial involving the United Kingdom arm of the European network for striatal transplantation ("NEST-UK") resulted in no serious side effect related to the operation [153]. This group also suggested a comprehensive, logical yet pragmatic screening program for future neural transplantation [154]. Meanwhile, the efficacy of fetal striatal cell transplantation was shown in another study group, in which four patients with HD have the stabilization or improvement of motor indices after fetal neuroblast implantation, and the graft has survived and developed striatal-like structures in the host brain [148].

Another large-scale study has been going on in a multicenter trial in France (NCT00190450).

This study group is the first to undertake their trial in accordance with the standardized core assessment protocol for intracerebral transplantation in Huntington's disease (CAPIT-HD), and detailed reports of transplantation in the first five patients have been published [145, 147, 155, 156]. In these series, three of the five patients showed motor and cognitive improvements two years after intracerebral fetal neural grafts, which were correlated with recovery of brain metabolic activity in grafted striatal areas and connected regions of the cerebral cortex, measured by fluorodeoxyglucose-positron emission tomography. Restoration of the lost sensory-evoked potentials is also noted. Furthermore, six years after transplantation, clinical improvements became plateaued and then fade off variably within 4–6 years while maintaining stable cognitive function. Cerebral metabolism has also deteriorated progressively, sparing the benefits in the frontal cortex and at the precise location of the grafts. This feature suggested that fetal neural transplantation provides a period of several years of improvement and stability, but not a permanent cure, and strategies of neuroprotection should be developed further [145]. Although it is still controversial, a recent study raised a possibility that the transplanted fetal striatal tissue can undergo disease-like neuronal degeneration after a decade

of implantation [157]. Suboptimal long-term graft survival might be caused by the allograft immunoreactivity, microglial responses, and cell-to-cell neurotoxicity [158]. Recently, donor-specific anti-HLA antibodies were detected in six out of 16 patients with HD who received human fetal striatal transplants [159]. These results underline the importance of careful approach for developing cell-based therapy in HD.

Apart from using human fetal striatal tissue, there was a clinical trial using porcine-derived striatal xenografts. In this case, the transplanted patients were treated with cyclosporin or a monoclonal antibody directed against surface major histocompatibility complex I molecules [160]. However, the surviving grafts were not detectable on MRI, and the treatment gave rise to no functional benefit for the patients [161]. In the case of xenografts, fully effective immunosuppression strategies should be resolved.

In order to use neural stem cells for clinical trials, several aborted human fetal tissues are required. Whether derived from elective or spontaneous abortion, there are sensitive ethical and social issues associated with using human fetal tissues for transplantation. There are also difficulties with accurate staging and collection (subject to appropriate ethical approval) and storage of fetal tissues [162-164]. Therefore, in most cases, they would never meet the levels of standardization and quality control required.

The delivery of trophic factors by genetically modified cells into striatum of patient has become another therapeutic approach in HD. A variety of growth factors, including the neurotrophins, fibroblast growth factor (FGF), ciliary neurotrophic factor (CNTF), glia-derived neurotrophic factor (GDNF), and brain-derived neurotrophic factor (BDNF), have been found to promote survival of striatal neurons in culture [117, 118, 165]. Direct injection of various trophic factors incorporated into viral vectors has problems of standardization, regulation, and longevity of treatment. Instead, implantation of engineered cells to express the desired transgene has been suggested [166]. Intracerebral administration of a device formed by a semipermeable membrane encapsulating a BHK cell line engineered to synthesize CNTF has been tried. No sign of CNTF-induced toxicity was observed, while improvements in electrophysiological results were observed. However, depression was observed in three out of six HD patients, and heterogeneous cell survival in the device hindered further clinical trials [166, 167]. Recently, mesenchymal stem cell engineered to secrete BDNF has been suggested, due to its clinically applicable characteristics [116].

7. Future directions of Huntington's Disease research and clinical applications

Therapeutic approaches using NSCs and other stem cell products for CNS diseases fall into two broad categories: (i) regenerative/cell replacement to promote host tissue repair mechanisms and/or to replace missing or damaged cells and (ii) therapeutic delivery of macromolecules (enzymes, cytokines, neurotrophins, drugs, etc.) for neuroprotection and/or stimulation of repair. However, because HD is a progressive neurodegenerative disease and stem cells might replace and protect only striatal neurons with limited capacity, stem cell therapy as

means to stop disease progression might be insufficient [168]. As such, future directions of cell therapy in HD should move beyond the replacement of lost neurons. To date, clinical trials have been undertaken with fetal donor tissue in the striatum in HD. For therapeutic efficacy, reconstitution of a functional dynamic information-processing circuit without ectopic connections using transplanted stem cells is necessary. Another major challenge is to achieve controlled differentiation of embryonic stem cells or induced pluripotent stem cells into specific neuronal phenotypes, such as medium spiny neurons in the absence of aberrant growth or tumor formation. Furthermore, novel approaches to provide therapeutic molecules for neuroprotection should also be tried and verified.

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