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Cell-based therapies for Huntington's disease

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Abstract

Cell-based therapies are a viable option for the long-term treatment of Huntington's disease (HD), which is characterized by progressive neurodegeneration predominately in the striatum and cortex. Current research focuses on genetic suppression of the mutant huntingtin (*mHTT*) gene and cell replacement therapy of the lost cells in the HD [LM1]. As we discuss here, the recent development of induced pluripotent stem (iPS) cells technology demonstrated the potential of cell-based therapy in rodent models. It was shown that iPSCs were capable of differentiating into lost neurons in HD and stem cell grafts can improve motor deficiency in HD rodent models. Altogether, these findings have shown great promise for developing the foundation of the cell-based therapy.

HD is an inherited single-gene dominant disorder caused by the abnormal expansion of CAG repeats in the *HTT* gene [1,2]. Excessive aggregation of mHTT proteins cause cell toxicity and apoptosis of the GABAergic projection neurons in the striatum and some glutamatergic neurons in the cortex [3]. Currently, there is no cure for HD. Efforts have focused on symptomatic treatment with drugs or gene therapy. The objective of gene therapy is to reduce the translation of toxic mHTT proteins through RNAi. To be most effective, RNAi treatment strategies need to be applied at the early stages of the disease; however, most patients do not develop symptoms and are not found to have the disease until severe degeneration of striatal neurons has already occurred. An alternative treatment is cell-based therapy, which replenishes the lost population of striatal neurons by transplanting neural cells intracranially into the striatum. In this review, we highlight new findings in gene and cell-based therapy within the past 2 to 3 years. We also discuss a combination approach

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that could be used to overcome the limitations of each individual technique, thus offering a more comprehensive therapy for HD.

Gene therapy: therapeutic suppression of *mHTT*

The ideal gene therapy approach for HD is to target and reduce specifically the transcript of the *mHTT* allele with RNAi or antisense oligonucleotides (ASOs) without influencing the normal *HTT* allele, thus maintaining HTT function [4–6]. Recently, studies have shown the feasibility and efficacy of reducing mHTT levels in HD cells. Amelioration of the key HD phenotypes correlates with the knock down of both mutant and normal alleles of the *HTT* transcript through RNAi in HD mouse models [7–10]. The Davidson group reported that short-hairpin RNA (shRNA), although more potent, resulted in higher levels of cell toxicity compared with miRNA, which showed better safety profiles in silencing of *HTT* in rodent models [7]. RNAi approaches that nonspecifically target both mutant and normal alleles have raised serious safety concerns. The normal physiological role of HTT remains largely unknown and *HTT* knockout mice are embryonically lethal; therefore, approaches that specifically target and reduce the *mHTT* allele, while maintaining clinically safe levels of the normal allele, are desirable [6,11–14].

ASOs, which are single-stranded oligodeoxynucleotides, can be used to target and suppress specifically the expression of the *mHTT* allele [15]. ASOs enter the cell and reduce gene expression by RNase-H-mediated degradation of the complementary mRNA [6,15]. ASOs bind complementary mRNA and physically block translation of the target mRNA [6,15]. One of the key benefits of ASOs is that they can target single nucleotide polymorphisms (SNPs), which differentiate the normal *HTT* allele from *mHTT* alleles, thus specifically suppressing the expression of the *mHTT* allele [4]. Pfister *et al.* demonstrated 22 predicted SNPs sites by sequencing and revealed three allele-specific SNPs that might be sufficient to cover most HD patients in certain populations [16]. In HD rodent and nonhuman primates (NHPs) models, sustained disease mitigation was achieved following a transient reduction of HTT expression using ASO infusion therapy [17]. These reports suggest that cells in which HTT expression is reduced by short-term ASO treatment, sustain reversal of the disease phenotype [11].

Challenges for gene therapy

One of the major obstacles in the application of RNAi- and/or ASO-mediated suppression of *mHTT* is the method of delivery [6]. Two methods have previously been used to deliver oligonucleotides invasively into selected brain regions. One involves repeated injections of oligonucleotides into the central nervous system. This approach is problematic because repeated injections are required over a prolonged period of time [6]. This can be overcome with a continuous injection delivery system. In a recent preclinical study in NHPs, an intraparenchymal catheter was implanted with a needle tip in the striatum and connected to a pump, which could be refilled and delivered continuously, in the abdomen [18]. The second option is to express the silencing oligonucleotides using viral delivery; however, this approach can lead to interference of normal cellular functions because of random insertion of the viral expression vector [6,19]. Instead of using an integration competent viral gene-

delivery vehicle for delivering oligonucleotides, adeno-associated viruses and integration-deficient lentiviruses have shown high infectivity and prolonged expression *in vivo* [20–22].

Another drawback is the overall effectiveness and safety of using RNAi and ASO methods to suppress mHTT expression. Concerns include the detrimental off-target effects, the loss of the normal *HTT* allele in nonspecific strategies, as well as the low potency that has been shown in limited studies using ASOs [6,11,19]. Finally, the most efficacious timing of gene suppression therapy in HD disease progression still remains to be determined. If treated at late stages with extensive neuronal loss, the target cell populations in the brain might be already lost; thus, early-stage treatment is required in gene therapy.

Cell-based therapy for HD

The objective of cell-based therapy for HD is to replenish the lost cells to reverse the disease phenotype or to delay disease progression over time. In general, cell sources that have been reported in HD cell-based therapy are fetal tissue cells, stem cells and neural progenitor cells.

Fetal cells therapy for HD

Several pioneer studies provide evidence that grafted fetal striatal tissue can successfully survive, differentiate into desired cell types, and integrate with the host cells in rodent and NHP HD models [23,24]. Successful cell therapy might not only improve basic motor and cognitive functions, but also the quality of life by restoring fine motor movement. In a rat HD model, forelimb movement patterns were repaired close to normal levels after cell transplantation [25]. Although some motor and cognitive improvements were found following transplantation in human, the improvements did not persist long term in clinical trials [26,27]. This indicates that the conditions of cell grafting still need to be optimized; for example, how to prepare fetal cells for transplantation. Cisbani *et al.* [28] investigated why the solid graft striatal tissues vanished through time in the host patients 9 or 12 years after transplantation. Large atrophic astrocytes surrounding the grafted tissues were observed as well as a lack of larger blood vessels in the grafted area. This suggests that insufficient trophic support leads to a low survival rate of grafted cells over time. In addition, the method of graft cells preparation might also affect cell viability. Single-cell suspensions of fetal striatal cells, instead of solid grafts, have shown an increased survival rate and vascularization in the rodent HD model [29]. However, fetal cells are derived from aborted fetal tissues; therefore, ethical concerns and limited donors have made this strategy less viable despite its therapeutic promise. Thus, increasing attention is focused on alternative approaches of using PS cells or neural progenitor cells (NPCs).

Stem cell and NPC therapy for HD

Embryonic stem (ES) or iPS cells have the ability to differentiate into cells from any of the three germ layers (ectoderm, mesoderm or endoderm). Human stem cell transplantations in both genetic and chemical lesion rodent HD models have shown success in replacing damaged cells [30,31]. Using immunofluorescence analysis (positive staining of β III-tubulin, GABA, GAD, and Meis2) and electrophysiological recording, Ma and colleagues

demonstrated that human ES cells were able to differentiate specifically into GABAergic neurons [31]. These neurons were also positive for DARPP32, which is a marker of medium spiny neurons (MSNs), which represent most striatal neurons. Ma *et al.* further transplanted the NPCs derived from human ES cells into a chemical lesion HD mouse model [31]. The transplanted cells not only survived, but also differentiated into GABAergic neurons in the mice striatum. These human GABAergic neurons made connections with host neurons and rescued the HD motor deficits after 16 weeks [31]. In another study, Carri's group successfully designed a new differentiation protocol following developmental principles. They induced both human ES and iPS cells by mimicking the normal neurodevelopment of the ventral telencephalon to generate NPCs, and further differentiated the NPCs into GABAergic neurons with similar identities of MSNs [32]. As shown by immunofluorescence staining, these neurons not only expressed typical MSNs neuronal markers, such as DARPP32, GAD65/67, GABA, CALB1, ARPP21, but also carried dopamine and adenosine receptors. These GABAergic neurons showed MSN properties by repetitive firing and a fast inactivating potassium current with a delay to the first spike [32]. Having transplanted these striatal NPCs into a chemical lesion HD rat model, Carri's group also showed the survival and differentiation of the NPCs and correction of drug-induced turning behavior after three weeks. However, a recent study showed that transplanted undifferentiated and predifferentiated human stem cells into a typical (R6/2) transgenic HD mouse model did not diminish disease progression [33]. This might be because of the short lifespan of the transgenic mice compared with the chemical lesion HD mice. Thus, detailed mechanisms underlying the cell transplantation still remain to be ascertained.

One of the advantages of choosing iPS cells as a therapeutic source is the ability to generate patient-specific NPCs, which can escape the immunological rejection of the patient's immune system after transplantation. The patient-specific cells will benefit the increased survival rate of the grafted cell in the brain, and evade the risk of immunosuppression treatment for the patients, including possible cytotoxicity, infection and tumor growth. However, details of the controlling factors for a successful cell therapy still need to be understood better to provide a more robust and safe clinical therapy.

Challenges for cell therapy

There are at least four major challenges for cell-based HD therapy: (i) determining the most ideal cell type for transplantation; (ii) safety issues relating to cell transplantation; (iii) the mechanisms by which the transplanted cells differentiate into correct cell types and integrate with host cells; and (iv) the migration of transplanted cells.

Ideal cell type

The most ideal cell types for transplantation are stem cells or progenitor cells, because, compared with fetal tissues, they are easier to obtain. Particularly, somatic cells from patients can be reprogrammed into iPS cells, which preserve the original cell identity. However, it means that the cells from the patient with HD will still carry *mHTT* genes, which will lead to cell death and, in turn, to a reoccurrence of the HD disease phenotype.

Major safety issues of cell transplantation

In 2013, a long-term study from the NEST-UK consortium evaluated the safety and efficacy of fetal cells grafted in five patients with HD after 3 to 10 years. They found that these striatal fetal tissues were safe after 10 years post-transplantation [27]. The same year, another group also reported no tumor formation from grafted cells in two patients with HD 9 and 12 years after cell transplantation [28]. However, from 2002 to 2010, there were a few cases reported that showed the grafted cells had overgrown in the patients following fetal cell transplantation [34]. When utilizing human ES cell transplantation into rat brains, two studies reported tumor formation of the grafted cells [35,36]. Therefore, neural stem cells (NSC) or NPCs, which are committed to a neuronal fate, might be needed to reduce the chances of tumor formation [31,32].

Mechanisms by which the transplanted cells differentiate into the correct cell type and integrate with host cells

Several studies in rodents were able to differentiate ES or iPS cells into GABAergic neurons and, more specifically, neurons with MSN properties [31–33,35]. However, the detailed mechanisms and the percentages of cells differentiated into neurons or astrocytes are still unclear. Furthermore, when and how the cells reach maturation and make functional synapses to the local neurons remains to be clarified.

The migration of transplanted cells

Stem cell fate and behavior varies *in vivo* and *in vitro*, including proliferation rate, lineage differentiation, gene expression patterns and influences of the microenvironment. Therefore, it is important to monitor grafted cells in a noninvasive way with a high spatial and temporal resolution.

A combination of gene therapy and neural progenitor cell therapy

We believe that a combination of gene and cell therapy (GET-NPT) (Figure 1) might be particularly promising. First, the somatic cells from patients with HD patients could be derived into iPS cells, which can then be differentiated into NPCs. Given that these HD-NPCs carry *mHTT*, RNAi or ASOs could be used to target *mHTT* alleles and suppress mHTT expression, which would reduce the accumulation of toxic mutant proteins. Second, the corrected HD-NPCs would then be transplanted back into the brain of the patient, thus reducing immunological rejection, replenishing the lost cell population and restoring neural function. Last, the transplanted NPCs would need to be monitored by a noninvasive reporter to ensure their long-term efficacy.

A noninvasive method of monitoring grafted cells *in vivo* after transplantation is crucial. This would provide a better understanding of the mechanisms of the survival and behavior (e.g. migration) of the grafted cells, as well as their integration at the graft site. Thus, the status of the cell graft could then be correlated with therapeutic outcome. Various methods have been used in monitoring transplanted cells *in vivo*. In small animals, luciferase or even red fluorescence protein have been used to track grafted cells using bioluminescence imaging (BLI) techniques. However, for larger animals, BLI can not be used because of the

thickness of the tissue. Therefore, to track grafted cells in larger animals, such as monkeys or humans, magnetic resonance imaging (MRI) and positron emission topography (PET) could be used. A report showed that grafts of hematopoietic stem cell could be monitored by PET for up to 32 weeks [37]. By contrast, MRI has unique advantages over PET and optical imaging technology. It can be used to image deep tissues with high spatial and temporal resolution [38–40]. However, transplanted cells cannot be monitored with MRI unless a contrast agent is used. Metal-chelate exogenous contrast agents and synthetic superparamagnetic iron-oxide (SPIO) nanoparticles have been used to improve contrast [40–46]. The limitation on monitoring time because of the dilution of the contrast agents as cells continue to divide has been a major problem [47]. Therefore, one of the best approaches is to develop a genetic reporter for MRI, such as the ferritin system [48,49]. Ferritin is an iron chelating protein that is involved in storing iron in a cell. However, low sensitivity and specificity hamper the use of the ferritin system in cell-tracking applications [49,50]. Also, long-term expression of ferritin levels in cells can cause toxic effects in cells that resembles age-associated neurodegeneration [50,51]. Another possible candidate is *MagA*, which is a bacterial gene involved in transporting iron and forming magnetite (Fe_3O_4) crystal [52]. Magnetite crystal is considered to be an excellent MRI contrast agent because it can induce relaxation time. *MagA*, which can be expressed in mammalian cell lines, forms magnetosomes and increases MRI contrast [47]. The most recent candidate for a genetic MRI reporter is the divalent metal transporter, DMT1 [53]. Unlike the aforementioned candidates, DMT1 provides positive signal enhancement, which improves sensitivity [53]. However, the cytotoxicity of expressing DMT1 in different cell types, especially for neurons, and the pharmacodynamics of delivering manganese to the brain need to be investigated further and optimized.

Concluding remarks

In this review, we have discussed current advances, specifically the pros and cons, of gene therapy and cell therapy. Studies demonstrated the therapeutic potential of reducing mHTT expression levels, laying the groundwork for developing strategies to correct HD cells genetically and mitigated disease-associated phenotypes. We advocate GET-NPT, which takes advantage of gene therapy to silence *mHTT* expression in patient-derived HD cells for autologous cell-based therapy. The corrected neural progenitor population can differentiate and propagate into mature neurons with similar morphological and electrical properties, and these cells can then integrate with host circuitry. GET-NPT might fulfill the need to replenish the lost cell population in the brain and hopefully rescue the HD phenotype by rebuilding functional neural circuit with the host cells. In addition, the first HD transgenic monkey model has been generated, which was shown to develop clinical features of HD similar to those seen in humans [54]. Disease phenotypes at the cellular (i.e. intranuclear inclusions and neuropil aggregates) [54,55] and behavioral (e.g. involuntary movement and coordinated movement deficiency) levels were observed in this model. Longitudinal studies show that HD monkeys develop neural morphometric changes that can be detected by MRI (e.g. striatum and hippocampal volume loss) and cognitive behavioral impairments related to hippocampal functions. Combined with the observations of cellular, pathological and cognitive behavioral abnormalities, it makes the transgenic HD monkey an ideal candidate

for testing GET-NPT in preclinical studies, which might reveal new avenues for combating HD.

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Highlights

- Specifically silencing *mHTT* can be accomplished by antisense oligonucleotides
- Successes in stem cells and NPC studies move cell-based therapy forward
- GET-NPT takes advantage of gene therapy in patient-derived cells for cell therapy
- Noninvasively monitoring the transplanted cells *in vivo* is crucial
- A transgenic HD monkey model is a suitable candidate for preclinical studies

Figure 1.

The combination of gene therapy and neural progenitor cell therapy (GET-NPT) for the treatment of Huntington's disease (HD). Induced pluripotent stem (iPS) cells from a patient with HD, which carry the mutant huntingtin gene (*mHTT*), can be derived into neural stem cells (NSC) or neural progenitor cells (NPCs). Mutant *HTT* expression in NSC and NPCs can be silenced by using RNAi or antisense oligonucleotides (ASOs), and monitored by MRI genetic reporter. The corrected cells can then be transplanted into brain of the patient to replenish the lost cell population.