

Chapter 2

Huntington's Disease and Cell Therapies: Past, Present, and Future

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Abstract

Huntington's disease (HD) is an inherited neurodegenerative disease that is characterized by movement abnormalities, cognitive impairment, and abnormal behavior as well as sleep and weight problems. It is an autosomal dominant disorder caused by a mutation in the huntingtin gene on the short arm of chromosome 4, which results in the progressive degeneration of the basal ganglia (caudate, putamen, and globus pallidus), cerebral cortex, brainstem, thalamus, and hypothalamus. This chapter considers four avenues of research: (a) the restoration of neurogenesis as an endogenous cell therapy in HD, (b) fetal tissue transplantation, (c) stem cell transplantation, and finally (d) the use of endogenous trophic factors such as brain derived neurotrophic factor.

Key words Huntington's disease, Cell therapy, Neurogenesis, Subventricular zone, BDNF, GDNF, CNTF, Transplantation, Mesenchymal stem cell, Neural stem cell, Neurotrophic factors, Immunosuppression

1 Clinical Features and Pathology

Huntington's disease (HD) is a devastating inherited neurodegenerative condition first described by George Huntington. In a paper that nowadays is considered a classic in the literature of neurology he explains: "It begins as an ordinary chorea might begin, by the irregular and spasmodic action of certain muscles, as of the face, arms, etc. These movements gradually increase when muscles hitherto unaffected take on the spasmodic action, until every muscle in the body becomes affected (excepting the involuntary ones), and the poor patient presents a spectacle which is anything but pleasant to witness" [1]. It is a disease characterized not only by movement abnormalities but also by cognitive impairment and abnormal behavior, as well as weight problems and sleep disturbances [2].

One of its prominent motor symptoms is chorea, derived from the Greek word *χορός* meaning dance-like. Other symptoms such as bradykinesia, although not necessarily detected at the early stages

of the disease, have been considered to constitute an important part of the motor aspect of HD [3]. Evidence for this was first provided by the fact that even after pharmacological suppression of chorea, motor function did not really improve [4–6]. Besides motor symptoms a whole range of other features is present in HD. Cognitive decline usually emerges at an early stage [7–9]. This includes executive dysfunction, which has been associated with striatal and insular atrophy [10]. Psychiatric symptoms are also prevalent, and relatively independent of the cognitive and motor aspects of the disease [11]. These include irritability and apathy, hallucinations, and depression [12–14].

HD can become manifest at ages from as young as 2 years to as old as 80 or more. Typically, however, it tends to strike in midlife [15], with progression over 15–20 years, the duration of disease being influenced by the age of symptom onset—running a shorter course in younger onset cases [16]. It is an autosomal dominant disorder caused by a mutation in the huntingtin gene (*htt*) on the short arm of chromosome 4 (4p16.3) [17]. This mutation is caused by an expansion of the CAG triplet (cytosine–adenine–guanine) that encodes for glutamine in the coding region of the first exon of the HD gene [2, 18], which has a normal range of up to 29 repeats. When these CAG repeats reach 40 or more the disease is fully penetrant, while incomplete penetrance occurs with 36–39 repeats [19, 20]. Repeats between 27 and 35 can be meiotically unstable during paternal transmission, and it has been known that descendants of men in this range can inherit CAG repeats of 40 or more [15]. This has been used to explain the phenomenon of anticipation in HD, whereby the age of onset of manifest disease becomes earlier in successive generations [21–23]. Huntingtin, in both wild-type and mutant forms, interacts with a variety of transcription factors [24]. Among the transcriptional pathways affected in HD, two have been studied extensively, namely, the cAMP responsive element (CRE) and specificity protein 1 (Sp1). The CRE pathway has a role in neuronal survival [25] and early down-regulation of CRE-regulated genes is a feature of early human HD [26]. There is a great deal of literature on the normal function of *htt*, which is still not completely understood.

A genetic test can reliably detect the size of CAG repeat length in the *htt* gene. This CAG repeat length has been associated with the expected age at which onset of the disease is most likely to occur [18, 21]. This relationship has been extensively reviewed by Langbehn and colleagues [27], who report that, for instance, a 40-year-old individual who has CAG repeat lengths over 41 has a 95 % chance of disease onset by the age of 70. Whether CAG repeat length can reliably predict the timing of disease onset as well as the rate of its progression [28] is a controversial topic.

Post-mortem studies have shown progressive degeneration of the basal ganglia, with prominent cell loss and atrophy in the

caudate and putamen but also in the cerebral cortex, brainstem, thalamus, and hypothalamus [2]. There is progressive loss of medium spiny GABAergic neurons in the striatum [29] as well as cortical and hippocampal neurons [30, 31]. The angular gyrus of the parietal lobe [32, 33] and lateral tuberal nuclei of the hypothalamus [34, 35] are also affected in HD patients. There is evidence of neuronal dysfunction even at the pre-manifest stage; loss of staining of various cytoskeletal elements in early stage HD tissue may be related to changes in neuronal morphology and consequently function [36, 37].

A standardized scale is the most commonly used clinical rating tool for describing the severity of disease manifestations. It was first introduced in 1979 and at that time consisted only of a functional scale [38]. The Unified Huntington's Disease Rating Scale (UHDRS) was introduced in 1996 as a team effort by the Huntington's Study group, and comprises motor, behavioral, functional, and cognitive domains [39]. As with any qualitative clinical scale, the UHDRS has its limitations. It is inherently non-linear and subjective, and there is considerable inter-rater and intra-rater variability [40].

2 Epidemiology

A number of studies of the epidemiology of HD in the UK have been published. In 1954 Pleydell [41] provided a detailed report on the county of Northampton: by tracing the available pedigrees, 61 cases were identified and within a year another choreic family was recorded [42], giving an incidence of 6.5 cases per 100,000 for that county. A number of similar studies followed [43–45]; a study carried out in an area of East Anglia found a much higher incidence of HD [46], 9.24 per 100,000 as opposed to the much earlier East Anglia study which gave an incidence 1.2 per 100,000 [47]. Similar studies in Ireland [48] reported a prevalence of about 6.4 per 100,000. Contrary to what George Huntington first reported—"the disease exists, so far as I know, almost exclusively on the east end of Long Island" [1]—a stable prevalence is observed in most populations of about 5–7 affected per 100,000 [49], with a few exceptions such as Tasmania [50] and the Lake Maracaibo [51] in Venezuela.

No treatment is currently available to slow or halt the unremitting and fatal progression of HD. To date work in HD cell therapy has been (a) to harness the ability of the brain to self-repair through the upregulation of endogenous stem cells/neurogenesis, (b) to replace dead and/or dying neurons through fetal or stem cell transplantation, and (c) to protect neurons vulnerable to disease progression through the administration of neuroprotective trophic factors via cell or viral delivery [52].

2.1 Restoring or Manipulating Neurogenesis as an Endogenous Cell Therapy in Huntington's Disease

Neurogenesis—the formation of new neurons—occurs normally in specific regions of the adult brain, namely, the subventricular zone (SVZ) adjacent to the caudate nucleus, and the hippocampus [53]. One proposed therapeutic strategy for HD is to upregulate endogenous neurogenesis in the hope that the extra cells thus produced could ameliorate disease symptoms and partially repair the damaged brain. Neural stem cells in the SVZ, dentate gyrus of the hippocampus, and also the olfactory bulb, can differentiate into all lineages of the adult central nervous system including neurons [54, 55]. Injury or neurodegeneration can upregulate proliferation and promote the migration of new cells to the damaged area [56–59]. But it remains to be clarified whether the observed increase in cell genesis is associated with any significant repair, and whether or not it might be of therapeutic value.

Adult neurogenesis has been extensively studied in both HD transgenic mice and humans. The R6 mice (R6/1 and R6/2) are the most studied animal models of HD. They harbor exon 1 of the human *htt* gene with respectively 115 and 150 CAG repeats [60]. The phenotypes of R6/2 mice mimic many of the human HD symptoms and thus provide a good animal model. A number of animal studies have reported that hippocampal neurogenesis is decreased in both R6/1 and R6/2 mice [61–64]. The molecular cascade by which proliferating hippocampal neural progenitors exit the cell cycle to become new neurons, migrate, and differentiate into functional and fully mature neurons is controlled by serial expression of a number of specific transcription factors. Neurogenin 2 and *neuroD1* demonstrate a critical role in controlling neuronal commitment and hippocampal granule neuroblast formation, both during embryonic development and in postnatal hippocampal neurogenesis [65–67]. R6/2 mice have shown impaired spatial learning using the Morris water maze [68]. Like HD patients afflicted by the disease, R6/2 mice have shown progressive learning impairments on cognitive tasks sensitive to frontostriatal and hippocampal function. Two studies have also indicated that reduced adult hippocampal neurogenesis leads to defective spatial learning and memory [69, 70]. Similarly, HD patients suffer from deficiencies related to spatial memory [71, 72]. Studies have shown that normal *htt* activity and *NeuroD1* are linked and are required for proper neurogenesis [73, 74].

Neurogenesis can be upregulated not only by neurotrophic factors but also by certain antidepressants. Indeed, it has been suggested that neurogenesis is important to the efficacy of antidepressants [75]. The antidepressant fluoxetine was used in treating R6/1 mice from 10 to 20 weeks of age [76]. Beneficial effects included the reversal of affective symptoms and improved cognitive performance. These were attributed to promotion of survival, differentiation, and/or functional integration of adult-born neurons rather than neural proliferation alone.

Fibroblast growth factor 2 (FGF-2) protects striatal neurons in toxin-induced models of HD, exerts a trophic effect on striatal neurons, and stimulates proliferation of striatal neural stem cells. It also regulates htt expression by cultured striatal neurons [77–80]. FGF-2 has been investigated in the R6/2 mouse model [81] where it was found to stimulate neurogenesis, induce migration of newborn cells into the striatum and cortex, and significantly extend lifespan. The nascent neurons that migrated into the affected striatum assumed phenotypic features of medium spiny neurons (the principal striatal cell type lost in HD) and extended processes to the globus pallidus, where spiny neurons normally project.

2.2 Fetal Tissue Transplantation

The idea that grafts of fetal striatal tissue could survive, differentiate toward a functional phenotype and be integrated into the host circuitry has been tested in a number of studies. The earliest transplantation study in an HD animal model occurred in 1983. Transplants of fetal rat striatal tissue fragments led to moderate functional benefits [82]. The first long-term demonstration that striatal allografts could survive, differentiate and integrate in the host striatum in a nonhuman primate model of HD came from Dunnett and colleagues [83], who also described a recovery of motor skills. Primary human fetal striatal cells also survived, migrated and differentiated into both neurons and glia, when used for xenograft experiments in the adult rat central nervous system [84].

In small groups of human HD patients, there have been transient clinical improvements of motor scores within 6 months of transplantation, followed by progressive clinical deterioration similar to the natural history of the disease [85–89]. Reports from long-term studies showed motor and cognitive improvement at 2 years, consistent with an increase in brain activity in the grafted striata and in frontal and prefrontal cortices. In one series of five patients, motor benefits plateaued for 4–6 years, followed by subsequent deterioration with disease progression [90]; cognitive stabilization lasted for more than 6 years in three out of five patients. In another study of two patients, one experienced improvement in both motor and cognitive functions which endured for 5 years, with increased striatal D2 receptor binding evident on 11C-raclopride (RAC) PET, suggesting long-term survival and efficacy of the graft [91]. Another study has reported shorter-term benefits in six out of seven patients, which did not last beyond 2–3 years [92].

Post-mortem analyses show grafted cell survival at 18 months [93] and 6 years post-transplantation [94]. In contrast, grafts analyzed 10 years after cell implantation demonstrated clear grafted cell degeneration in a pattern similar to the disease itself, including preferential loss of grafted striatal projection neurons and preservation of interneurons [89]. The similarity of the pattern of degeneration in the striatum in HD and then in striatal components of genetically unrelated neural grafts suggests that some of the pathogenic

events underlying neuronal death in HD are also responsible for the long-term degeneration of genetically unrelated transplanted cells [89].

Findings from all these studies indicate that striatal neuronal transplantation might provide a period of improvement and stability but it is by no means a permanent cure for the disease [95]. Implantation of fetal grafts in adult HD brain aims to substitute for lost cell populations and not to oppose the progression of neurodegeneration. In addition to the eventual graft degeneration, as the disease progresses other regions of the brain become affected, including the neocortex. Implants in the striatum alone are unlikely to be effective at this stage.

A number of issues need to be addressed before the initiation of future clinical trials. First, there is no consensus on the optimal method of tissue preparation. The fetal brain dissection methods utilize different regions of the Ganglionic Eminence (GE), although all include regions rich in projection neurons. Some methods optimize inclusion of more projection neurons, others maximize inclusion of cholinergic interneurons [96]. The amount and cellular composition of the transplanted cells must be regulated [97], as transplants with less than 30 % striatal content are ineffective. Secondly, some studies [92, 94] have described acute neurosurgical complications with subdural hematoma and intracerebral bleeding. No such subdural hematomata have been reported in the Parkinson's disease literature. Brain atrophy increases the risk of subdural hematoma, and Hauser has suggested [92] that advanced HD patients with significant brain atrophy be excluded from surgical trials, to minimize the risks involved in such procedures.

The use of fetally derived striatal grafts for transplantation in patients with HD raises obvious ethical issues because of the need for aborted fetal tissue. This has been part of the impetus towards the development of stem cells as a graft material.

2.3 Stem Cell Transplantation

The idea of stem cell therapy for HD has received increasing attention over the last decade. Stem cells are easier to obtain than primary fetal tissue and have the potential to be manipulated to eliminate possible problems of graft rejection. Neural stem cells (NSCs) can be isolated from the fetal, neonatal, and adult brain and propagated in culture [98]. Grafted NSCs exhibit physiological properties of mature intrinsic pyramidal neurons and become functionally integrated into host neural circuitry [99]. Transplantation of neural stem cell into a transgenic mouse model after neuronal ablation survived, migrated, differentiated, and improved memory impairment [100].

Stem cells derived from various other sites have been tested in HD animal models. Bone marrow stem cells (containing both hematopoietic stem cells [HSCs] and mesenchymal stem cells [MSCs]) were implanted bilaterally into the quinolinic acid (QA)

damaged striatum of HD rat models, remained viable for at least 37 days, and significantly reduced functional deficits in working memory [101]. Transplantation of MSCs alone resulted in a decreased atrophy of rats QA-lesioned striatum. These results confirm the potential of bone-marrow derived mesenchymal stem cells in treatment of microanatomical defects in motor disorders of HD [102]. However, in most of these studies, only a few cells (1 %) expressed neural phenotypes, and it was suggested that MSCs worked as neurotrophic enhancers via the release of growth factors, therefore allowing surviving cells within the caudate to function more efficiently and to facilitate other compensatory responses [103]. Another study [104] demonstrated significant engraftment of undifferentiated exogenous mesenchymal or neural stem cells throughout the lesioned area in an HD rat model, as late as 8 weeks post-transplantation. The stem cell factor (SCF), strongly upregulated within host cells in the damaged striatum, was able to activate the SCF receptor c-kit and its signaling pathway and to promote the migration and proliferation of mesenchymal and neural stem cells in vitro. Furthermore, the c-kit receptor blockade altered neural stem cell distribution within the lesioned striatum. Taken together, these data demonstrated the importance of factors such as stem cell factor, produced in situ in the lesioned striatum, to promote the migration and engraftment of MSCs via the SCF receptor c-kit.

In another study, in a 3-NP model of early HD, adult peripheral precursor cells from Sertoli cells (testis-derived cells with immunosuppressive and trophic properties) were transplanted into rat striatum. Results indicated that the Sertoli transplants were able to ameliorate locomotor abnormalities [105]. However, one problem with autologous cell grafts may be that they carry the mutant *htt* gene responsible for the disease. There are a number of problems related to cell survival, cell fate (for example avoiding teratoma formation), maintenance of a defined differentiated phenotype, and proper cell engraftment in transplantation [106]. The differentiation of stem cells or treatment with growth factors in vitro prior to implantation may facilitate fate determination while reducing the risk of tumor formation, a primary concern when using stem cells [107, 108]. A study by Dihne et al. used ES cell-derived aggregates consisting predominantly of β -tubulin neurons, which demonstrated that the state of maturity of ES cell-derived transplants critically determined tumorigenicity [108].

MSCs are currently the most widely investigated adult cells for brain cell therapy. However, their neuronal differentiation potential remains very low or uncertain after transplantation. The poor cell survival and engraftment observed when using chromaffin cells, hRPE cells, MSCs, and in general all kinds of transplanted cells, has called into question the efficacy of such procedures. These issues may now be addressed by tissue-engineering approaches [106].

Stem cell therapy for the treatment of HD patients is an exciting emerging area of research. Animal studies show promise, but translation to the bedside is still in its infancy.

2.4 Using Endogenous or Exogenous Trophic Factors in HD Cell Therapy

Neurotrophic factors are large molecules that do not cross the blood–brain barrier. Manipulation of both endogenous and exogenous trophic factors has been used in HD therapy. Transplanted stem and progenitor cells can promote the survival of host cells by releasing trophic factors such as brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), and glial cell line-derived neurotrophic factor (GDNF) [109, 110].

BDNF is known to be of specific importance for differentiation and survival of striatal neurons [111–113]. BDNF knockout mice recapitulate the striatal gene expression phenotype of human HD [114]. Based on striatal gene expression, BDNF models, both heterozygous and homozygous knockouts, seem to be more like human HD than the other HD models. This implicates reduced trophic support as a major factor contributing to striatal degeneration in HD. Because the majority of striatal BDNF is synthesized by cortical neurons, the data from this study also suggest that cortical dysfunction contributes to HD's hallmark effects on the basal ganglia. Environmental enrichment at 5 months of age ameliorated motor symptoms and prevented loss of body weight induced by the HD transgene. BDNF levels remained unaltered by the disease in the anterior cortex, implying that enrichment might prevent HD-induced impairment of anterograde transport of this neurotrophin to the striatum [115]. As a whole, these results suggest that regulation (either through endogenous or exogenous manipulations) of abnormal BDNF production have the potential to improve motor function.

Ciliary neurotrophic factor was one of the first purified trophic factors that was demonstrated to protect striatal output neurons (especially vulnerable GABAergic striatal neurons) in an adult HD animal model [116–118]. In one study, direct intrastriatal delivery was achieved by bilaterally implanting encapsulated baby hamster kidney (BHK) cells genetically engineered to produce human CNTF [119]. This not only protected neurons from degeneration but also restored neostriatal functions. Ciliary neurotrophic factor is likely to be more beneficial if administered at the early stages of the disease, when infusion of CNTF into the striatum might not only block the degeneration of neurons but also could alleviate motor and cognitive symptoms associated with persistent neuronal dysfunction.

The glial cell line-derived neurotrophic factor (GDNF) family is differentially regulated by excitotoxic insults in the striatum [120]. GDNF protects striatal medium spiny GABAergic neurons from excitotoxic injury in a rodent model of HD [121, 122]. Viral-mediated gene transfer of GDNF into the striatum of

presymptomatic transgenic HD mice provides neuroanatomical and behavioral protection such as preservation of neuronal cells from degeneration, and a reduced percentage of neuronal cells with mutant htt inclusions [123, 124].

2.5 Future Directions

Post-mortem results indicate that neuronal transplants undergo disease-like degeneration by 10 years after transplantation [125], and any therapeutic effect disappears in less than half this time. The mechanisms by which nonmutant huntingtin-bearing transplanted tissue becomes affected by the disease process are unclear. Immune mechanisms may play a role [126], and immunosuppression, essential to prevent rejection of transplants elsewhere in the body, is used inconsistently [96]. The grafts may suffer from various other insults, and a better understanding of the culprit processes might permit their eventual pharmacological treatment. Improvement of the graft survival time is a key issue, and neurotrophic factors may have an important role in preserving grafts as well as native tissue; repeated transplantation is unlikely to be a realistic option, as accurate and safe stereotactic graft placement will become more difficult with progressive brain atrophy, increasing risk and decreasing the chance of success. It is not clear whether fetal cells or stem cells will be superior, and for the present research on the two continues in parallel. Other graft-related issues that need further research include the methods of preparation of fetal tissue (including the exact region of the ganglionic eminence that fetal cells are taken from), and the optimal implanted dose (cell numbers) and form (solid graft or cell suspension).

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