Stem Cell Treatments for Huntington’s Disease

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July 2011
Volume 1
Issue 1
Doctors Academy Publications

The World Journal of Medical Education and Research (WJMER) is the online publication of the Doctors Academy Group of Educational Establishments. Published on a quarterly basis, it’s aim is to promote academia and research amongst all members of the multi-disciplinary healthcare team including doctors, dentists, scientists, and students of these specialties from all parts of the world. The principal objective of this journal is to encourage the aforementioned from developing countries in particular to publish their work. The journal intends to promote the healthy transfer of knowledge, opinions and expertise between those who have the benefit of cutting edge technology and those who need to innovate within their resource constraints. It is our hope that this will help to develop medical knowledge and to provide optimal clinical care in different settings all over the world. We envisage an incessant stream of information will flow along the channels that WJMER will create and that a surfeit of ideas will be gleaned from this process. We look forward to sharing these experiences with our readers in our subsequent editions. We are honoured to welcome you to WJMER.
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This review will critically consider the evidence that supports the use of stem cells in the management of Huntington’s Disease (HD) including that provided by animal models.

HD is a chronic progressive neurodegenerative condition associated with motor, cognitive, and psychiatric symptoms. It has a prevalence of 4-8 per 100,000 and is caused by an autosomal dominant mutation in the Huntingtin gene (HTT) located at 4p16.3, which codes for the protein Huntington. Part of the HTT gene contains a repeated trinucleotide sequence of the bases CAG, which encodes a polyglutamine chain; the diagnosis of HD is confirmed by the detection of an expansion of >36 CAG repeats coupled with a positive family history and characteristic clinical features. Patient’s become symptomatic between ~35 - 44 years and the average survival time is 15 to 18 years thereafter.

Unfortunately current licensed treatments for HD are limited to symptom control and palliation. Stem cells offer a new dimension that provides insights into; understanding the genomics and proteomics of HD potentially identifying drug targets; providing a cellular HD model to validate gene therapies such as those based on RNAi; and providing a source of human striatal cells for transplantation. Such principles have been applied to animal models of HD. These will be discussed in turn.

Both human embryonic stem- (ES) and induced pluripotent stem- (iPS) cells from affected donors have been used as cellular models to understand the molecular mechanisms of HD. Mutant HD ES cell lines with CAG expansions in the adult-onset range of ~40-51 repeats and iPS cell lines, which include some with CAG triplet repeat lengths associated with juvenile onset HD, are available from laboratories. Studies using these cell lines have reliably reported the replication of known molecular pathological mechanisms although the relevance of these findings is limited for two reasons. Firstly “age equivalence”, that is discrepancies in the chronobiology of the in vitro ES- and iPS cells, which are immature in relation to “developmental age” compared to their vivo situation in HD patients whereby the disease process is developmentally more mature having a late clinical age of onset. This maybe important as RNA processing may be controlled differently in the embryo relative to adults and gene expression could be dependent upon developmental age. Secondly, human HD ES- and iPS cell lines provide a disease specific cellular model that is inherently biased towards cell autonomous mechanisms. Therefore, validating transcriptomic results from HD ES- and iPS- cells in vitro by comparison against transcriptomic results of the in vivo model in the HD patient is not clear-cut.

HD-specific iPS cell neural derivatives have been used for assaying new drugs that disrupt cell-autonomous mechanisms of HD. These cells can be used to validate gene therapy and provide an ideal alternative to the ‘gold standard’ that is HD brain tissue, which is difficult to obtain and limited to post-mortem samples. RNAi using shRNA and small synthetic oligonucleotide RNA molecules targeted against mutant HTT mRNA silences the HTT gene by inhibiting its translation. In a mouse HD model this resulted in improved motor symptoms and longevity. HD-specific iPS cell neural derivatives are now being used to escalate validating gene therapy even further via “allele specific RNAi”, which involves using synthetic oligonucleotides to suppresstranslation of mutant HTT leaving normal levels unaltered. The results of these trials are awaited. This may be limited by varying levels of basal HTT gene expression in different neural cell types.
ES-, adult- and IPS- cells can all be used as a source of striatal cells for transplantation in HD. These will be discussed in turn.

Recent evidence from a rodent model showed that human ES-cell derived striatal grafts produced neural precursors capable of differentiating into DARPP-32 expressing (a dopamine receptor marker) GABAergic neurons. These extensively integrated into host neuronal circuits contributing to dopaminergic and glutamatergic neurotransmission within the midbrain and cortex respectively with a resultant functional rescue of motor deficits. The ES-cell derived striatal grafts showed no evidence of tumorigenesis at 16 weeks post-transplantation.

Adult stem cells have been used as a source of striatal cells for transplantation in HD. In a rat model of HD, adipose-derived stem cells from human subcutaneous tissue transplanted into the striatal border were found to improve behavioural symptoms and slowed striatal degeneration. Further evidence has shown that intra-striatal transplantation of homotypic foetal tissue improved functional symptoms in HD patients. However, adult stem cells have a limited role in cell transplantation for HD due to a lack of donor tissue. Furthermore, there are logistical difficulties associated with the acquisition and preparation of foetal stem cells and thus very few patients have benefited from foetal stem cell transplantation. The results of large on-going clinical trials looking at the role of foetal stem cells in HD are awaited.

Transplanted IPS cells derived from a patient with juvenile onset HD carrying 72 CAG repeats regenerated GABAergic striatal neurons and when transplanted into a rat model of HD significantly improved behavioural symptoms. Limitations included: the IPS cells had a lower neuronal differentiating capability compared to ES cells; and the hope of IPS cells providing a cure for HD was hindered by the post-transplantation observation that IPS cells are prone to proteasome inhibition with subsequent development of HD pathognomonic features. The aforementioned evidence embodies the importance of transgenic animal models in developing stem cell treatments for HD with the aim that stem cell derivatives can, in the first instance, repair the brain of HD transgenic animal models and then ultimately that of human HD patients. The criteria of what constitutes a reasonable transgenic animal model of HD should include: age and time-dependence, that is demonstrating a gradual and progressive decline in striatal neurons; an ability to measure the motor, cognitive and behavioural impairment associated with HD; and demonstrable pathognomonic hallmarks of HD such as polyglutamine neuronal inclusions and striatal degeneration. These principles are exemplified by the R6/2 transgenic mouse model of HD, which is created by transfecting exon 1 of the human HD gene containing expanded CAG triplet repeats into the murine germ line. These transgenic mice replicate many features of human HD. Tests such as the fixed speed rotarod test can measure functional impairment due to motor deficits and similar tests exist for quantifying cognitive and psychiatric symptoms. Post-mortem studies on the brain of R6/2 transgenic mice have identified polyglutamine neuronal inclusions that existed before symptom onset. These neuronal inclusions occurred prior to any selective neuronal cell death being identified.

A study looked at the effects of transplanting the C17.2 neural stem cell line into the lateral ventricle of R6/2 transgenic mice. Trehalose was co-administered to inhibit polyglutamine aggregate formation. The effects of this combined treatment on the R6/2 transgenic mouse model included: reduced polyglutamine aggregate inclusions; reduced striatal volume and ubiquitin-positive aggregation; and increased life expectancy. Motor function improved as measured by behavioural evaluation.

In addition to transplantation therapy, R6/2 transgenic mice have been used as a model for screening other therapies for HD. These novel therapies include: antagonism of histone methylation and deacetylation, caspase inhibition, inhibition of excitotoxicity, inhibiting oligomerization and misfolding of protein aggregates, environmental fortification, improving metabolic symptoms including hyperglycaemia, transglutaminase inhibition, antioxidant medications, genetic manipulations, and restoring neurogenesis. Results from phase I and II clinical trials on these new drug discovery targets have been disappointing with no clinical interventions tested in murine models significantly delaying HD progression.

The results of studies using transgenic HD animal models are limited in their application. R6/2 transgenic mouse models express, as a third allele, fragments of or full length HTT protein. As the cause of striatal degeneration in HD involves both “a toxic gain of function” of the mutant HTT and “a loss of function” of the normal HTT, transgenic mouse models such as R6/2 fail to ‘model’ the pathology and clinical phenotypes that result from the loss of human wild-type HTT and the expression of full-length mutant HTT. Furthermore, xenotransplantation experiments involving transgenic mouse HD models are capricious, which makes extrapolating the significance of results to human HD patients difficult. Differences in size of the human striatum relative to the rodent striatum considerably changes the extent of proliferation of neuronal stem cell derivatives needed and the spatial
ability of graft-derived neurites to integrate into host neuronal circuits and contribute to dopaminergic and glutamatergic neurotransmission within the midbrain and cortex respectively. Finally as the age of onset of HD in humans is “35-44 years, the short two-year lifespan of a mouse limits its usefulness as a transgenic HD model.

In summary, stem cells have offered a hope, which has now turned to an expectation that developing curative therapies for HD are within the realms of possibility. However, until a credible and tested human stem cell neural model of HD is created then the discrepancies between promising data from experimental animal models and clinical studies will continue to be a barrier that hinders the search for a cure.

References:

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