ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

HUNTINGTON DISEASE

INTRODUCTION

Huntington's disease (HD) is a fatal, dominantly-inherited neurodegenerative disorder characterized by movement abnormalities, behavioral and personality changes, and often psychiatric manifestations and cognitive decline. HD is caused by a CAG triplet repeat expansion in the huntingtin gene (HTT), which encodes an expanded polyglutamine stretch in the huntingtin protein. While all cell types of the body express mutant HTT, its major deleterious effects appear target a few regions of the forebrain. As a result, HD is characterized by the selective loss of striatal medium spiny neurons (MSNs) in the brain's basal ganglia, a region of the forebrain concerned with motor coordination and control, as well as by the loss of neurons in the deep layers of the cerebral cortex. In addition, patients with HD experience early and progressive loss of myelin in the forebrain white matter, which reflects dysfunction of the brains' glial support cells, oligodendrocytes and astrocytes. The regionally-confined nature of brain pathology in HD suggests that it might be responsive to cell-based therapy.

RATIONALE AND EXPERIMENTAL EVIDENCE OF CELL-BASED THERAPIES FOR HD

A number of groups have pursued the hypothesis that striatal neuronal replacement may prove beneficial to HD patients. Initial clinical efforts using fetal tissue showed at best transient benefits. More recently, efforts using neural stem cells to restore striatal cell populations have enjoyed some success in experimental animals, as have efforts focusing on glial cell replacement using human glial progenitor cells. The latter approach proved effective at rescuing threatened medium spiny neurons in HD transgenic mice, and were effective at normalizing both the electrophysiological and behavioral phenotype of these mice; the transplanted HD mice manifested slowed disease progression and extended survival, indicating that glial progenitor cell transplantation might serve to delay disease progression in HD. Alternative strategies are under development using gene therapeutic approaches to induce the production of new neurons from resident neural stem cells. These approaches may be combined with glial cell replacement to improve outcome. Additionally, antisense oligonucleotide therapies are currently in trials which work by lowering the expression of mutant huntingtin protein. These latter approaches look promising and could be used in tandem with these cell therapeutic strategies to slow or halt disease progression, while both restoring lost cells and rescuing lost neurological function.

WHAT IS THE CLINICAL STATUS OF CELL-BASED THERAPIES FOR HD?

To date, there is no effective treatment for HD. Over the past few years, researchers have focused on both the role of neuronal and glial dysfunction in causing neuronal and synaptic dysfunction of HD. As a result, both neural and glial transplantation-based strategies, using progenitor cells produced from human pluripotent stem cells, are under intensive preclinical development. These studies have strongly suggested the therapeutic potential of a cell replacement strategy in HD, whether accomplished by neural or glial progenitor cells. As a result, efforts are now underway in several centers to produce clinically-appropriate populations of both neural and glial progenitor cells for intracerebral transplantation in symptomatic HD patients.

WHAT DOES THE NEAR FUTURE HOLD?

Neural and glial progenitor cell differentiation protocols are both reliable and scalable, allowing the production of cells appropriate for clinical transplantation. Whereas trials of glial transplantation in HD may be expected in the near future, longer term efforts will likely include the combination of glial engraftment with gene therapy induced neurogenesis, or as combined with transplants of medium spiny neuronal progenitors, perhaps together with the concurrent use of mutant huntingtin-lowering strategies. Such combination strategies will likely be critical to achieving a successful clinical outcome.

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March, 2019