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Potential of Stem Cell Transplantation for Huntington's Disease

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Short commentary

Neurodegenerative diseases, such as Alzheimer's disease (AD), Huntington's disease (HD), and Parkinson's disease (PD), are highly disabling and fatal disorders affecting millions of people worldwide and are defined as progressive and uncontrolled progressive loss of motor neuron function or neuronal cell death [1]. Chronic neurodegeneration may develop for a long time and lead to the loss of specific neuronal subtypes or the general loss of neuronal populations. In the brain, AD and HD cause extensive neuronal loss, while PD involves the specific and local loss of dopaminergic neurons in the substantia nigra. Although these conditions show unique neuronal pathologies, the exact mechanisms of neuronal loss are complex, making it difficult to determine effective treatments. The lack of effective therapies for these diseases greatly impacts both patients and their caregivers and creates an enormous burden on society.

Recently, cellular therapy has earned increasing attention as a potentially feasible novel therapy. Stem cells are an attractive option as they are self-renewing while retaining the ability to produce differentiated phenotypes. During the ontogeny and development of humans and animals, stem cells with high renewal ability and multidirectional differentiation potential exist in both embryo and adult tissues. Stem cells can be isolated, amplified, and cryopreserved in vitro, and can be induced to differentiate into a variety of cells and tissues under appropriate conditions, which provides an ideal model system for exploring developmental biological issues such as human and animal embryogenesis, tissue cell differentiation, gene expression regulation, and so on. Scientific problems provide an ideal model system, and at the same time open up new ways for cell replacement therapy and gene therapy for clinical tissue defect diseases and genetic diseases. At present, stem cells have made progress in the treatment of blood diseases, surgical diseases, neurological diseases, and other clinical diseases.

The major sources of stem cells currently for potential therapeutic use in neurodegenerative diseases include embryonic germ cells (ESCs) derived from the gonadal ridge of the fetus [2] or the inner cell mass of embryos [3], mesenchymal stem cells (MSCs) derived from mesoderm [4], induced pluripotent stem cells (iPSCs) [5], and the more lineage-restricted sources such as neural stem cells (NSCs) derived from the fetal [6], neonatal [7] or adult [8] brain. Although the efficiency of the neurodegeneration potential of stem cell therapy is not precise, ESCs and NSCs are suggested as excellent cell sources for stem cell therapy.

HD is a hereditary disease with the progressive and fatal neurodegenerative disorder of neurons in the brain, characterized by involuntary movements (chorea), behavioral impairment, cognitive decline, and psychiatric disturbances including, prominently, depression [9,10]. It is caused by an expansion mutation of the cytosine-adenine- guanine (CAG) repeat within exon one of the huntingtin (IT15) gene, identified in 1993, encoding a 350 kDa protein termed Huntingtin (HTT) [11]. In healthy individuals, CAG triplet repeats 10-35 times, while mutant alleles containing >36 CAG repeats are likely to cause HD. The onset time depends mainly on the repeat length, but also genetic modifiers [12,13] and environmental factors [14]. HD affects about 5 people per 100,000 in the United States, Europe, and Australia [15], with onset at about 40 years of age, and relentlessly develops to complete dependence and death in about 15-20 years [16,17].

In HD, the earliest and major histopathological features are the loss of striatal medium-sized spiny neurons (MSNs) due to the cytotoxic effects of the mutant Huntington protein and the disruption of cortical and basal ganglia circuits. However, as the disease progresses, neurons in the cerebral cortex, hippocampus, thalamus, globus pallidus, hypothalamus, subthalamic nucleus, substantia nigra, and thalamus are also lost [18-20]. As with other neurodegenerative diseases, patients with HD requires multidisciplinary medical facilities to intervene in symp-

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toms. However, no proven therapy for HD that can mitigate its devastating clinical course is available, and most pharmacological treatments are palliative. Therefore, stem cells have long been considered as a promising therapeutic resource for HD that can replace the lost striatal MSNs [21]. This has been demonstrated by Victor and colleagues [22] who transplanted four transcription factors enriched in the developing striatum, CTIP2, DLX1, DLX2, and MYT1L (CDM) that synergized with miR-9/9*-124 into the striatum of immunodeficient mice, the reprogrammed human cells differentiated into neurons, with membrane properties equivalent to native MSNs, exhibited long-term conversion stability and persisted for over 6 months in vivo, and expressed dense dendritic spines and long axonal projections to the anatomical targets of MSNs. Moreover, a previous study investigated the therapeutic effects of neural precursor cells derived from a human iPSC line (1231A3-NPCs) on the quinolinic acid (QA)-lesioned rat model of HD and reported that 1231A3-NPCs transplanted animals showed significant behavioral improvements for up to 12 weeks based on the stepping, staircase, rotarod, cylinder, and apomorphine-induced rotation tests. Further, 1231A3-NPCs could survive up to 13 weeks post-transplant and restore striatal MSNs [23].

In addition, in-vitro-differentiated stem cell-derived human striatal progenitors could undergo maturation and integrate into host circuits upon intra-striatal transplantation. Axon growth to the appropriate target regions is critical to the correct reconstruction of the lost circuits and the long-term therapeutic benefits. A recent study detected the expression of human Neural cell adhesion molecules (hNCAMs) in serial sections of transplanted HD model rats and the entire rostrocaudal extension of the forebrain to the substantia nigra, and the results showed that the transplanted stem cell-derived human striatal progenitors could extend projections to the appropriate target structures, including the subthalamic nucleus, the globus pallidus, and the substantia nigra, and receive synaptic contact from both host and graft cells, which contributed to a significant improvement in sensory-motor tasks up to 2 months post-transplant [24].

Stem cells hold great potential in HD therapy, not only in terms of stem cell-based therapies but also as a means to investigate the cellular and molecular mechanisms of HD pathophysiology by using cell reprogramming and gene-editing techniques. Cell reprogramming allows for the study of HD-specific molecular pathways in MSNs, and for investigators to consider not only the role of HTT but also genetic modifiers that play an important yet unknown role in the pathology of HD [21]. In a subsequent study [25], researchers reported that human iPSCs derived from HD patient fibroblasts could be corrected by homologous recombination to replace the amplified CAG repeats with normal repeats, and this correction persists in the differentiation of iPSC into DARPP-32 positive neurons in vivo and in vitro. In addition, the correction of HD iPSCs normalized the pathogenic HD signaling pathway (BDNF, cadherin, transforming growth factor-β, and caspase activation) and reversed disease phenotypes, such as cell death susceptibility and neural stem cells mitochondrial bioenergetic changes. The results represented a significant advance in the application of HD iPSCs for stem cell replacement therapy and the construction of human HD cellular models with the same human genetic background. Interestingly, Molero and colleagues [26] demonstrated that BACHD:CAG-CreERT2 mice, carrying mutant HTT modified to harbor a floxed exon 1 and containing the pathogenic polyglutamine expansion, displayed similar pathological features of HD to BACHD transgenic mice expressing mutant HTT throughout life, such as early vulnerability to N-methyl-D-aspartic acid (NMDA)-mediated excitotoxicity, temporally distinct abnormalities in striatal electrophysiological activity, striatal neurodegeneration, impairments in motor coordination, and altered corticostriatal functional connectivity and plasticity.

Stem cell therapy is also expected to be used in the treatment of HD as, in addition to the possibility of cell replacement, they can mediate a variety of pathogenic pathways through the paracrine release of a series of neuroprotective and immunomodulatory factors [21]. Given that BDNF has been demonstrated for multiple animal models of HD and in the human HD brain, researchers transplanted human embryonic stem cell-derived NSC line into the striatum of HD model mice, which resulted in a significant increase in BDNF and synaptophysin, a synaptic marker, levels of NSC-treated mice compared with the vehicle [27]. The results suggested that engrafted NSCs may improve synaptic connectivity by increased neurotrophic effects, including BDNF. A recent study investigated the effect of a clonal, conditionally immortalized neural stem cell line (CTX0E03) on rescuing deficits seen in an animal model of HD. In the study, researchers transplanted the CTX0E03 into the quinolinic acid-lesioned rat model of HD and then measured the behavioral changes with the rotarod, stepping, and staircase tests. Their results showed that compared with the sham- or fibroblast-transplanted group, transplantation of CTX0E03 gave rise to a significant behavioral improvement. In addition, they also found that CTX0E03 transplantation increased endogenous neurogenesis and angiogenesis, as well as reducing glial scar formation and inflammation [28].

Conclusion

In conclusion, while it has taken time, the revolutionary advances in stem cell transplantation therapy may finally provide the light at the end of the tunnel for HD patients and result in a therapeutic strategy to alleviate this debilitating disorder.

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