Review

Pathogenesis and potential therapeutic application of stem cells transplantation in Huntington’s disease

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ABSTRACT

Huntington’s disease (HD) is a progressive neurodegenerative disorder which is caused due to repetitive CAG or glutamine expression along the coding region of the Huntington gene. This disease results in certain movement abnormalities, affective disturbances, dementia and cognitive impairments. To this date, there is no proper cure for this rare and fatal neurological condition but there have been certain advancements in the field of genetic animal model research studies to elucidate the understanding of the pathogenesis of this condition. Currently, HD follows a certain therapeutic approach which just relieves the symptoms but doesn’t cure the underlying cause of the disease. Stem cell therapy can be a breakthrough in developing a potential cure for this condition. In this review, we have discussed the pathogenesis and the efficacy and clinical practicality of the therapeutic application of stem cell transplantation in Huntington’s disease. The application of this groundbreaking therapy on genetically altered animal models has been listed and analyzed in brief.

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1. Introduction

Neurodegenerative diseases are a process of deterioration in the intellectual and cognitive function of the central nervous system due to chronic progressive loss of structure [1]. Those diseases are responsible for contributing to about 6.3% of all diseases [2]. Neurodegenerative diseases such as Alzheimer’s disease (AD), Parkinson’s disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington’s disease is generally observable in the elderly population. But the causes associated with such degradation are poorly understood. For the heterogeneity of those diseases and as the clinical symptoms vary with the region of brain injury, the therapeutic medicines approved by Food and Drug Administration (FDA) fail to halt disease progression and extend life span (see Fig. 1).

When there is no available pharmacological treatment that offers long-term efficacy, recent progress in stem cell research shows great promise for the field. Human embryonic-derived stem cells and induced pluripotent stem cells, specifically recent advances in multipotent adult stem cells, are helping to design therapeutics for those diseases and replace lost motor neurons through autologous cell transplantation [3].

To understand the therapeutic value of stem cells, it is essential to understand the pathogenesis of different neurodegenerative diseases. In this review, we will discuss the pathogenesis and the efficacy and clinical practicality of the therapeutic application of stem cell transplantation in Huntington’s disease.

2. Stem cells and properties

Cells that can reiterate them continuously and differentiate themselves into various cell types are known as stem cells. There are two types of mammalian stem cells embryonic stem cells (ESCs), and adult stem cells (ASCs) found in different adult tissues. A new stem cell has been introduced with these two types of stem cells called induced pluripotent stem cells (iPSCs). It is possible to develop iPSC from other kinds of cells, including fibroblasts [4]. ESCs are derived from the undifferentiated inner mass cells of a human embryo competent in producing all the specialized tissues present in the human body. ASCs are undifferentiated non-reproductive cells derived from specific differentiated tissues in human bodies. As ASCs are non-reproductive cells, it is also known as somatic stem cell. There are a few types of ASCs; among them, Mesenchymal Stem Cells (MSCs) and Neural Stem Cells (NSCs) are used in different therapeutic applications. iPSCs are derived in the laboratory in a medium between ESCs and ASCs. Among those stem cells, embryonic stem cells (ESCs), MSCs, brain-derived neural stem cells (NSCs), and induced pluripotent stem cells (iPSCs) have been used in neurodegenerative disease research.

3. Pathophysiology

Huntington’s disease (HD) is an inherited neurodegenerative disorder that occurs for selective neurodegeneration in the striatum, results in a range of cognitive and physical symptoms [5]. It is

Fig. 1. HD iPSCs possible therapeutic approaches in humans.
an autosomal dominant disease caused by a mutation in the huntingtin gene (HTT). This mutation causes a CAG trinucleotide repeat above a critical threshold of 35 times in exon1, where the number of repetitions is 18 in a healthy individual [6,7]. Translation of this CAG repeat in HTT results in expanding the polyglutamine (poly Q) tract at the N-terminus of the huntingtin gene. This Poly Q expanded HTT (mutant HTT, mHTT) gives rise to the toxic function phenotype such as cytotoxicity and biochemical dysfunction in HD [8]. There is various disruption in transcription, disorders in axonal transport, and impairment in proteostasis are assumed as a result of the mHTT protein.

3.1. Expansion of polyglutamine and cleaved in toxic fragments

Human HTT is predicted to be composed of HEAT repeats, consisting of about 50 amino acids formed of antiparallel z-helices with a helical hairpin configuration assembled into a superhelical structure with a continuous hydrophobic core [9]. Some unstructured regions interspersed in these HEAT repeats contain cleavage sites for proteolytic fragmentation and post-translational modification responsible for conformational changes of the protein and alternation of protein—protein interactions [10,11]. This conformational change generates large protein clusters that can be visualized by light microscopy [12]. In the different experimental environments, those expansions of polyQ in HTT show a connection with the aggregation. Though the globular spherical structure derived from Electronic Microscope’s data didn’t show any significant difference between the general population- Q23 and disease population Q46 and Q78 [13]. Another hypothesis says that, as HTT is involved in various protein—protein interactions and the formation of multi–protein complexes, dysregulation in this interaction for the polyQ expansion can be responsible for resultant phenotypes in HD. More specifically, mutant polyglutamine-containing peptide molecules accumulate in the nucleus of neurons and interact with different transcription factors and affect their functions [14].

In the Heat repeat of Human HTT, a polyglutamine stretch (polyQ) is located at the N-terminus. Different proteolytic cleavage such as caspase 6 and various proteases creates a range of toxic N-Terminal fragments [15]. Besides this, the aberrant splicing of the first exon of huntingtin protein count as an alternative mechanism for creating mutant fragments [16]. Those mutant fragments correlate with the increasing toxicity made by the formation of nuclear versus cytoplasmic less-toxic aggregates, which might contribute to differences in cell susceptibility [17–19].

3.2. Disruption in transcription and alternation in gene expression

One of the primary pathogenic mechanisms is disruption of transcription and alternation in gene expression. Several studies on DNA microarrays found that the transcription factor has altered gene expression profile [20,21]. This finding suggests that polyglutamine expansion interferes in alternation as the activation domain of various transcription factors is composed of glutamine-rich regions [22]. mHTT also affects the cell proliferation system by interacting with multiple regulators of transcriptions such as p53, cAMP response element-binding protein, and CREB-binding protein [23].

Recent studies showed that in HD, alternation of the genes is possible beyond transcription by regulating non-coding RNA. While studying the CBP, a transcriptional coactivator with histone acetyltransferase (HAC) functions, deregulation of histone modifications in HD was identified [24]. It has shown that expanded polyglutamine can disrupt histone acetylation activity by binding with the HAC domain of CBP [25]. As a result, it impacts histone deacetylase (HDAC) inhibitors, an inhibitor that prevents neurodegeneration in cells [26,27].

| Name of the drug | Therapeutic class | Mode of Action | References |
|-----------------|------------------|---------------|------------|
| Tetrazenzine    | VMAT2 Inhibitors | Modulation of dopaminergic signaling | [28,29] |
| Olanzapine      | Atypical antipsychotic | Suppress involuntary movements in HD patient | |
| Amantadine      | Glutamate antagonist | Management of chorea | [30] |
| Rivastigmine    | Acetylcholinesterase Inhibitor | Reduced dyskinesia | [31,32] |
| Fluoxetine      | Selective Serotonin Reuptake Inhibitor | Improvement in cognitive impairment | [33] |
| Baclofen        | GABAa agonist | Improvement in functional disability | [34] |
| Nabilone        | Cannabinoid | Management of depression due to HD | [35] |

From the aforementioned drugs, we can understand that these are used just for alleviating the symptoms of HD. Due to the absence of understanding of the major biological function of wildtype HTT completely, eradication of the expression of mHTT from affected tissue is critical for drug discovery [37]. However, from various clinical studies and research, it has been established that cell therapies can potentially restore tissue atrophy. Hence, stem cell therapy can be a flourishing therapeutic strategy as a targeted approach to replace the dysfunctional cells in HD.

5. Stem cell therapy for Huntington’s disease

The conventional therapies are given for the ease of symptoms [38]. These are not effective for an extended period and don’t respond well to every patient. For the lack of proper therapeutic, cell-based approaches have emerging potential for designing therapeutic strategies to modulate neuropathology that can modify disease age of onset or disease course. Several stem cells therapies have gained approval for clinical usage for a variety of CNS diseases. The advantages of stem cells’ ability to accurately mimic the normal cell repair and development process in the brain drive researchers to explore a new avenue for treating neurologic disease [39]. Different types of stem cells, including mesenchymal stem cells...
(MSCs), fetal neural stem cells, neural cell types differentiated from induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESCs), have been transplanted into a model for assessing the therapeutic potential [40–42].

5.1. Mesenchymal stem cells

For stem cell transplantation therapy for HD, adipose-and bone marrow-derived MSCs have a wide application for their capacity to release neurotrophic factors and the ability to differentiate into a wide variety of cell types [43]. MSCs can create a neuroprotective microenvironment by releasing specific ILs and cytokines, which is another reason behind its wide use [44]. More those stem cells are immune privileged and not tumorigenic as they are not pluripotent [45].

There have been several clinical studies in rodent models using multiple sources. Those studies showed an improvement in motor function and anxiety-like behaviors [46]. Some studies showed the ability to expand the lifespan [47] of these rodent model animals by decreasing the striatal lesion size, less neuronal and medium spiny neuron loss, stimulation of endogenous neurogenesis, and reduct of huntingtin aggregation [47].

Some studies helped to hypothesize that MSCs may provide in lieu of neuronal differentiation such as trophic support, specifically BDNF and immunomodulation [48]. Brain-derived neurotrophic factor (BDNF) decreases in patients with HD, and MSCs were implanted to overexpress BDNF into the striatum of YAC128 mice; some behavioral and pathological deficits were reduced [49].

5.2. Pluripotent stem cells

Human PSCs, both embryonic and induced patient fibroblasts, can be differentiated into neural cells with Medium spiny neurons (MSNs) characterization. For neuronal conversion, PSCs first acquire neuroectoderm fate by exiting the pluripotent state. So, generating a desired neuronal cell type involves the induction of the regional neuroepithelial phenotype (region-specific progenitors), which arises in the target cells [50]. As in the cultured sample, GABA-evoked currents and typical firing patterns of MSNs and interneurons are present; it creates the opportunity to elucidate disease mechanisms in HD and screen new candidate therapeutics [51]. It was a significant challenge in MSCs that the immune system used to destroy newly transplanted cells, but iPSCs obviate the need for immunosuppression as patient-derived autologous cells are transplanted, which can differentiate into any cell type.

In several studies, transplantation of iPSCs derived from somatic cells had demonstrated improvement in behavior and motor abilities in rodent HD models when mouse iPSCs from a healthy mouse were implanted into striata of 10-month-old YAC128 mice [52]. In addition, BDNF protein and receptor levels significantly increased in the striatum.

As in HD cause for mutation in a cell, it is necessary to modify before transplantation to avoid taking on the HD phenotype. In such a study, iPSCs were transplanted into unilateral QA-lesioned mice after being differentiated into GABAergic striatal neurons. After 33 weeks, they showed behavioral and motor recovery with the formation of mhtt aggregates [53].

5.3. Embryonic stem cells

Embryonic stem cells are derived after a week of fertilization where the cells develop into tissues and organs [54]. In transgenic mouse models, it has been determined that the ESCs can differentiate into neurons, oligodendrocytes and astrocytes which can potentially play a huge role in enhanced neuronal function and brain development [55]. The transplanted ESCs differentiate into neurons of the QA animal model and it has been observed to migrate around cortical regions showing recovery of the behavioral symptom. Further studies are required in this study because there is a possibility of adverse effects like the rejection of the immune response and tumor progression through human ESCs. There is also an ethical issue which can arise from using human embryos [56].

5.4. Neural stem cells

For a long time, the brain was considered to be a fixed system as neuronal division is not possible. But due to the advancement of technology, Neural Stem Cells were discovered to generate from the hippocampus and later from olfactory bulbs, striatum, spinal cord and septum. These cells can produce offspring cells which differentiate into neurons and glial cells [57]. For cell therapy for HD, primate and rodent models have shown remarkable possibilities. The NSC transplants have shown improvement in motor function, breakdown of aggregate formation and improved lifestyle [58]. IV administration of NSCs causes induction of functional recovery by migrating to the striatum and decreases striatal atrophy in rodent lesion models of HD [59]. NSCs can be ideal for the treatment of HD for which further research is very essential but the presence of ethical limitations might be a drawback in the development of this cell therapy.

6. Animal models of HD

The animal models are chosen based on the mimicking ability of the neuropathology as well as the symptoms of the disease. The animal models must represent the mechanisms and genetic pathway that leads to neurodegenerative processes in human disease. Hence the transgenic or gene-transferred animal models have to share the same defect in genes as human HD patients. Since the main concern is a mutation in htt gene, there must be a genetic alteration of the same gene in the animal models to be studied [60].

| Animal model | Species | HD pathway and symptoms | Type of stem cell therapy | Effect of stem cell therapy | References |
|--------------|---------|-------------------------|---------------------------|-----------------------------|------------|
| R6/2 mice | Transgenic mice | MSN degradation at the end stage, striatal atrophy, ventricular enlargement, unable to gain weight | BDNF-MSC | Increased life span | [61,62] |
| iPSC | | | | Enhanced immune response | [63] |
| ASC | | | | Normalized caspase pathway, BDNF, TGF beta and cadherin | [64] |
| NSC derived from human fetus | | | | Improved cognitive and motor behavior | [65] |

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7. Conclusion and future perspective

This article reviews several stem cell-based neural repair strategies and their positive effects on neurological, cognitive, and electrophysiological alterations in different rodent models of HD. Though with varying types of results with different kinds of stem cells on other rodent models, it is still confusing which approach will serve as the best therapy but as it is possible through stem cell reprogramming technology to generate patient-derived cellular models of HD it can help us in multiple ways such as understanding the pathogenesis of the disease and finding out potential therapeutic approaches.

Recently, Allogeneic MSC engraftments in macaque monkeys have been shown to have varying success due to immunogenicity, which can help us frame the future perspective of stem cell transplantation on Huntington’s disease. With the overcome of the obstacle of developing long-term cellular therapy, it will be possible to focus on the clinical follow-up with patients to demonstrate the safety and feasibility of this therapy by following the same safety profile they have shown preclinically. It will be possible to develop MSCs to act as a biological delivery system, enabling researchers to test different therapeutic targets for gene delivery using a reliable delivery platform.

Astrocytes and oligodendrocytes are widely known to release trophic factors that support the growth and repair of partner neurons, it is necessary to study how stem cells can help these two kinds of cells, which will open more possibilities for using stem cells in HDs therapeutic application.

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### Table: Stem Cell Therapy Effects on HD Models

| Animal model | Species | HD pathway and symptoms | Type of stem cell therapy | Effect of stem cell therapy | References |
|--------------|---------|-------------------------|---------------------------|----------------------------|------------|
| N171-82Q mice | Transgenic mouse | MSN degradation at the end stage, striatal atrophy, ventricular enlargement, unable to gain weight | Mouse ESC derived NPC or NSC | Reduced mhtt aggregation, Increased expression of BDNF, Improvement in motor functions like gait performance and rotarod | [66,67] |
| YAC128      | Transgenic mouse | 128 GAC repeats from human HTT | Adipose MSC derived from patients | Improvement in rotarod performance | [69,70] |
| CAG140      | Knock-in mouse | 140 polyglutamate repeats to mouse HTT | Mouse ESC derived NPC or NSC | Improved immune response, Increased expression of BDNF, Improved motor function | [71,72,73] |
| QA lesioned mice | All species | Mimicking of striatal histopathology of HD | iPSC-NSC derived from patients | Improved motor and behavioral functions, Reduced mhtt aggregation, Increased expression of BDNF | [74,75] |
| QA Rat      | Sprague Dawley and Fischer | Mimicking of striatal histopathology of HD | Mouse ESC derived NPC | Improvement in motor functions like gait performance and rotarod | [67] |
| 3NP-lesioned rats | All species except Fischer | Impairment of mitochondrial function resulting in cell death | Mouse ESC derived NSC | Improvement of spatial working memory, Reduction of striatal lesion, Reduction of inflammation, Prevention of loss of MSNs | [74,76,77] |
|             | Fischer | Impairment of mitochondrial function resulting in cell death | MSC | Improvement of motor function | [78,79,80] |

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### Authors’ contribution

YA conceived the study, YA and SP designed the study. YA supervised the study. SS and MD wrote the preliminary draft manuscript. YA and SP reviewed the preliminary draft manuscript. SS, MD, YA and SP edited, revised, and finalized the manuscript. All the authors read and approved the manuscript.

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### Data availability statement

This is a review article, and no new data were generated or analyzed in this study. Therefore, data sharing does not apply in this article.

### Ethics approval and consent to participate

Not applicable.

### Conflict of interests

The authors declare no conflict of interests.
References

[1] Chen W, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep 2016;13:3391–6. https://doi.org/10.3892/MMR.2016.4948.

[2] Alkhatr A, Andleeb A, Waris TS, Bazzar M, Moradi AR, Awan NR, et al. Neurodegenerative diseases and effective drug delivery: a review of challenges and novel therapeutics. J Control Release 2021;330:115–67. https://doi.org/10.1016/j.jconrel.2021.11.021.

[3] Thomsen GM, Gowing G, Svendsen S, Svendsen CN. The past, present and future of stem cell clinical trials for ALS. Exp Neurol 2014;262:127–37. https://doi.org/10.1016/j.expneurol.2014.02.021.

[4] T K, Y S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126:663–76. https://doi.org/10.1016/j.cell.2006.07.024.

[5] V JP, M D, Huntington disease. J Neuropathol Exp Neurol 1998;57:369–84. https://doi.org/10.1093/jnen/57.4.369.

[6] A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. The Huntington's Disease Collaborative Research Group. Cell 1993;72:971–83. https://doi.org/10.1016/0092-8674(93)90585-E.

[7] S A, K D, C J, B EK, R F, et al. CAG size-specific risk estimates for intermediate allele repeat instability in Huntington disease. J Med Genet 2013;50:650–6. https://doi.org/10.1136/jmg-2013-011921.

[8] H RJ, T YF. Proteostasis in Huntington's disease: disease mechanisms and therapeutic opportunities. Acta Pharmacol Sin 2018;39:754–69. https://doi.org/10.1038/s41496-018-0026-4.

[9] L W S, L C, WJ, R DC, H JA. Expression and characterization of full-length human huntingtin, an elongated HEAT repeat protein. J Biol Chem 2006;281:15916–22. https://doi.org/10.1074/jbc.M511007200.

[10] M A, T AA, W L, P E, S JS, F KH. Histone deacetylase inhibitors reduce polyglutamine toxicity. Nat Cell Biol 2007;9:2522–31. https://doi.org/10.1038/ncb1685.

[11] Nucifora Jr Frederick C, Sasaki Masayuki, Peters Matthew F, Huang Hui, W CL, E LM, G CA, R D, W S, G RK, et al. Caspase cleavage of mutant huntingtin in cultured human lymphoblast cell lines and human brain. J Cell Physiol 2002;188:405–14. https://doi.org/10.1002/jcp.10120.

[12] R T, O RN, J M, C R, C E, S JC, et al. Post-translational modifications in Huntington's disease: past experiences and future challenges. Stem Cell Res Ther 2015;6. https://doi.org/10.1186/1328-7241-6-248.

[13] Saha, M.J. Dey, S.K. Promon et al. Regenerative Therapy 21 (2022) 406-412.
stem cells and the function of Islet-1. Nature Communications 2014;5. https://doi.org/10.1038/NCOMMS5444.
[51] DC A, O'M, CV, FA, PS, TS, TM, et al. Human pluripotent stem cell differentiation into authentic striatal projection neurons. Stem Cell Rev Reports 2013;9: 461–74. https://doi.org/10.1007/S12015-013-9441-8.
[52] Al-Gharibeh A, Culver R, Stewart AN, Srinageshwar B, Spelke K, Frollo L, et al. Induced pluripotent stem cell-derived neural stem cell transplantations reduced behavioral deficits and ameliorated neuropathological changes in YAC128 mouse model of Huntington's disease. Front Neurosci 2017;11:628. https://doi.org/10.3389/FNINS.2017.00628.
[53] I, L, N, J, JY, PH, PR, KS, M, J, et al. Neuronal properties, in vivo, and pathology of a Huntington's disease patient-derived induced pluripotent stem cells. Stem Cells 2012;30:2054–62. https://doi.org/10.1002/STEM.1135.
[54] Mesheror E. What are embryonic stem cells and how can they help us? Front Young Minds 2020;8. https://doi.org/10.3389/FRYM.2020.00032.
[55] Li M, Pevny L, Lovell-Badge R, Smith A. Generation of purified neural precursors from embryonic stem cells by lineage selection. Curr Biol 1998;8: 971–4. https://doi.org/10.1016/S0960-9822(98)70399-9.
[56] Song J, Lee ST, Kang W, Park JE, Chu K, Lee S, et al. Human embryonic stem cell-derived neural precursor transplants attenuate apomorphine-induced rotational behavior in rats with unilateral quinolinic acid lesions. Neurosci Lett 2007;423:58–61. https://doi.org/10.1016/J.NEULET.2007.05.066.
[57] Neural stem cell | biology | Britannica n.d https://www.britannica.com.
[58] Johann V, Schiefer J, Sass C, Mey J, Brook G, Krüttgen A, et al. Time of transplantation and cell preparation determine neural stem cell survival in a mouse model of Huntington's disease. Exp Brain Res 2007;177:458–70. https://doi.org/10.1007/s00221-006-0689-y.
[59] Ming GL, Song H. Adult neurogenesis in the mammalian central nervous system. Annu Rev Neurosci 2005;28:223–50. https://doi.org/10.1146/ANNUREV.NEURO.28.051804.101459.
[60] Holley SM, Kandjou T, Reiling JC, Fury B, Coleal-Bergum D, Bauer G, et al. Therapeutic effects of stem cells in rodent models of Huntington's disease: review and electrophysiological findings. CNS Neurosci Ther 2018;24:329. https://doi.org/10.1111/CNS.12839.
[61] Mangiarini L, Sathasivam K, Seller M, Cozens B, Harper A, Hetherington C, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell 1996;87: 493–506. https://doi.org/10.1016/S0092-8674(00)81369-0.
[62] Pollock K, Dahlenburg H, Nelson H, Fink KD, Cary W, Hendrix K, et al. Human mesenchymal stem cells genetically engineered to overexpress brain-derived neurotrophic factor improve outcomes in Huntington's disease mouse models. Mol Ther 2016;24:965. https://doi.org/10.1038/MT.2016.12.
[63] An MC, Zhang N, Scott G, Montoro D, Wittkop T, Mooney S, et al. Genetic correction of Huntington's disease phenotypes in induced pluripotent stem cells. Cell Stem Cell 2012;11:253. https://doi.org/10.1016/J.STEM.2012.04.026.
[64] Lee ST, Chu K, Jung KH, Im WS, Park JE, Lim HC, et al. Slowed progression in models of Huntington disease by adipose stem cell transplantation. Ann Neurol 2009;66:671–81. https://doi.org/10.1002/ANA.21788.
[65] El-Alkawy G, Ratnay I, Johannsson SM, Gale R, Bates G, Modo M. Implantation of undifferentiated and pre-differentiated human neural stem cells in the R6/2 transgenic mouse model of Huntington's disease. BMC Neuroscience 2012;13:97. https://doi.org/10.1186/1471-2202-13-97.
[66] S G, B MW, S AH, J HA, D K, K JA, et al. Intranuclear inclusions and neuritic aggregates in transgenic mice expressing a mutant N-terminal fragment of huntingtin. Hum Mol Genet 1999;8:397–407. https://doi.org/10.1093/HMG/8.3.397.
[67] Zimmermann T, Remmers F, Lutz B, Leschik J. ESC-derived BDNF-overexpressing neural progenitors differentially promote recovery in Huntington's disease models by enhanced striatal differentiation. Stem Cell Rep 2016;7:693. https://doi.org/10.1016/J.SCIENTR.2016.08.016.
[68] Ebert AD, Barber AE, Heins BM, Svendsen CN. Ex vivo delivery of GDNF maintains motor function and prevents neuronal loss in a transgenic mouse model of Huntington's disease. Exp Neurol 2010;224:155–62. https://doi.org/10.1016/J.EXPNEURO.2010.03.005.
[69] Slow FJ, van Raamsdonk J, Rogers D, Coleman SH, Graham RK, Deng Y, et al. Selective striatal neuronal loss in a YAC128 mouse model of Huntington disease. Hum Mol Genet 2003;12:1555–67. https://doi.org/10.1093/HMG/DDG169.
[70] Im W, Lee ST, Park JE, Oh HJ, Shim J, Lim J, et al. Transplantation of patient-derived adipose stem cells in YAC128 Huntington's disease transgenic mice. PLoS Curr 2012;4. https://doi.org/10.1371/CURRENTS.RRN1183.
[71] Al-Gharibeh A, Culver R, Stewart AN, Srinageshwar B, Spelke K, Frollo L, et al. Induced pluripotent stem cell-derived neural stem cell transplantations reduced behavioral deficits and ameliorated neuropathological changes in YAC128 mouse model of Huntington's disease. Front Neurosci 2017;11. https://doi.org/10.3389/FNINS.2017.00628.
[72] Menalled LB, Sison JD, Dragatis I, Zestlin S, Chesselet MF. Time course of early motor and neuropathological anomalies in a knock-in mouse model of Huntington's disease with 140 CAG repeats. J Comp Neurol 2003;465:11–26. https://doi.org/10.1002/CNE.10776.
[73] Reiling JC, Relano-Gines A, Holley SM, Ochaba J, Moore C, Fury B, et al. Human neural stem cell transplantation rescues functional deficits in R6/2 and Q140 huntington's disease mice. Stem Cell Rep 2018;10:58. https://doi.org/10.1016/J.STEMCR.2017.11.005.
[74] Shear DA, Dong J, Haik-Creguer KL, Bazzett TJ, Albin RL, Dunbar GL. Chronic administration of quinolinic acid in the rat striatum causes spatial learning deficits in a radial arm water maze task. Exp Neurol 1998;150:305–11. https://doi.org/10.1006/exnr.1997.6657.
[75] Jeon I, Lee N, Li JY, Park IH, Park KS, Moon J, et al. Neuronal properties, in vivo, and pathology of a Huntington's disease patient-derived induced pluripotent stem cells. Stem Cells 2012;30:2054–62. https://doi.org/10.1002/STEM.1135.
[76] Lescoudran L, Unni D, Dunbar GL. Autologous adult bone marrow stem cell transplantation in an animal model of huntington's disease: behavioral and morphological outcomes. Int J Neurosci 2003;113:945–56. https://doi.org/10.1080/00207450390207759.
[77] Carpenter MK, Winkler C, Fricker R, Emerich DF, Wong SC, Greco C, et al. Generation and transplantation of EGF-responsive neural stem cells derived from GFAP-HFP transgenic mice. Exp Neurol 1997;148:187–204. https://doi.org/10.1006/exnr.1997.6676.
[78] Borlongan CV, Koutouzis TK, Sanberg PR. 3-Nitropionic acid animal model and Huntington's disease. Neurosci Biobehav Rev 1997;21:289–93. https://doi.org/10.1016/S0149-7634(96)85019-2.
[79] Rossignol J, Boyer C, Lempereur X, Fink KD, Thnard R, Blanchard F, et al. Mesenchymal stem cell transplantation and DMME administration in a 3NP rat model of Huntington's disease: morphological and behavioral outcomes. Behav Brain Res 2011;217:369–78. https://doi.org/10.1016/J.BBR.2010.11.006.
[80] Ryu JK, Kim J, Cho SJ, Hatori K, Nagai A, Choi HB, et al. Proactive transplantation of human neural stem cells prevents degeneration of striatal neurons in a rat model of Huntington disease. Neurobiol Dis 2004;16:68–77. https://doi.org/10.1016/J.NUBO.2004.01.016.