Regenerative Therapy 21 (2022) 406–412

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

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

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ARTICLE INFO

Article history:
Received 12 July 2022
Received in revised form
29 July 2022
Accepted 2 September 2022

Keywords:
Huntington's disease
Stem cells transplantation
Pathogenesis
Therapeutics

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.

Contents

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Peer review under responsibility of the Japanese Society for Regenerative Medicine.

https://doi.org/10.1016/j.reth.2022.09.001

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

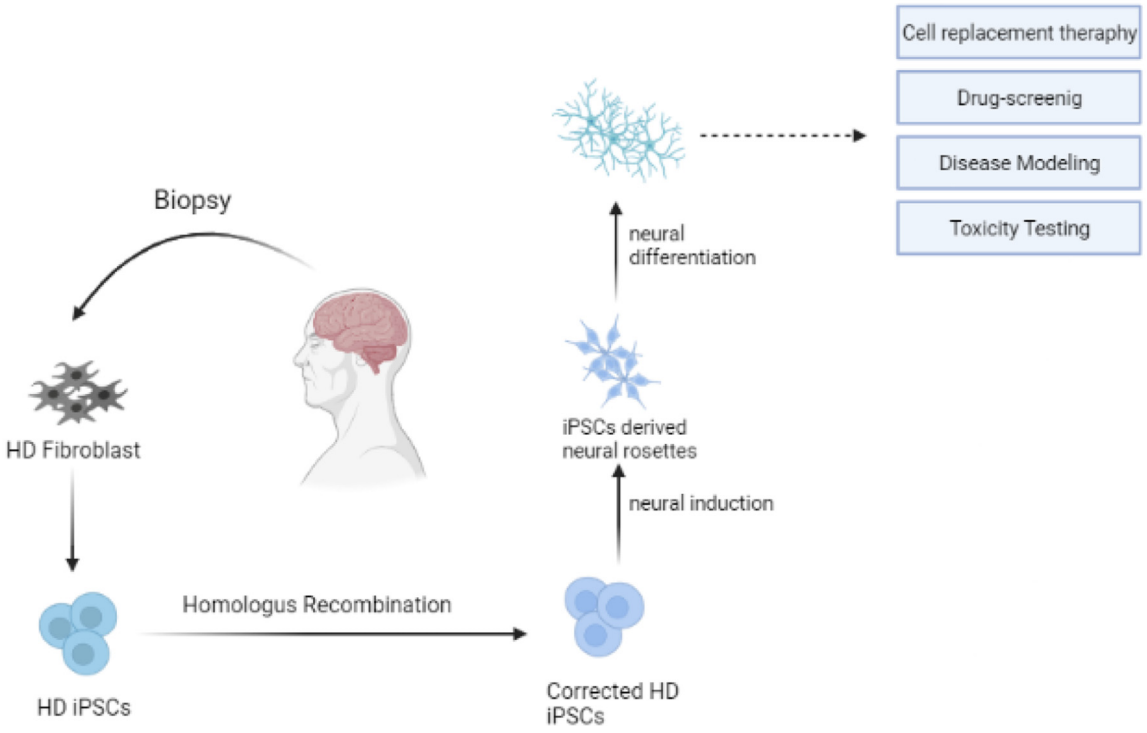

Fig. 1. HD iPSCs possible therapeutic approaches in humans.

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 transportation, 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 α-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].

4. Therapeutic approach towards HD

The treatment of HD is more symptomatic because no therapy might be able to target the underlying pathology of HD. The basic treatment goals are to provide relief, reduce the symptoms and improve the quality of life. Non-pharmacological interventions include-speech, physical and occupational therapy. Since HD is a progressive disorder, drugs are required along with non-pharmacological treatment for the ease of symptoms. Here is a list of the drugs below-

Name of the drug	Therapeutic class	Mode of Action	References
Tetrabenzine	VMAT2 Inhibitors	Modulation of dopaminergic signaling Suppress involuntary movements in HD patient	[28,29]
Olanzapine	Atypical antipsychotic	Management of chorea	[30]
Amantadine	Glutamate antagonist	Management of chorea Reduced dyskinesia	[31,32]
Rivastigmine	Acetylcholinesterase Inhibitor	Improvement in cognitive impairment Improvement in functional disability	[33]
Fluoxetine	Selective Serotonin Reuptake Inhibitor	Management of depression due to HD	[34]
Baclofen	$GABA_B$ agonist	Reduces chorea	[35]
Nabilone	Cannabinoid	Reduces chorea	[36]

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 reduction 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 therapies [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 Enhanced immune response	[61,62]
			iPSC	Normalized caspase pathway, BDNF, TGF beta and cadherin	[63]
			ASC	Improvement in limb clasping and rotarod Decreased aggregation of mhtt	[64]
			NSC derived from human fetus	Improved cognitive and motor behavior	[65]

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Animal model	Species	HD pathway and symptoms	Type of stem cell therapy	Effect of stem cell therapy	References
				Reduced mhtt aggregation Increased expression of BDNF	
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	Improvement in motor functions like gait performance and rotarod	[66,67]
			Mouse ESC derived GDNF-NPC	Enhanced survival of neurons in striatum Improvement in rotarod performance	[68]
YAC128	Transgenic mouse	128 GAC repeats from human HTT	Adipose MSC derived from patients	Late improvement of rotarod performance	[69,70]
		Striatal neuron degeneration	BDNF derived MSC	Enhanced immune response	[62]
			Mouse derived iPSC-NSC	Improved motor function Increased expression of BDNF	[71]
CAG140	Knock-in mouse	140 polyglutamate repeats to mouse HTT	Mouse ESC derived NPC or NSC	Enhanced synaptic connections with host cells	[72,73]
		Loss of striatal volume		Improved motor and behavioral functions Reduced mhtt aggregation Increased expression of BDNF	
QA lesioned mice	All species	Mimicking of striatal histopathology of HD	iPSC-NSC derived from patients	Behavioral improvement and recovery	[74,75]
			Mouse ESC derived NPC	Improvement in motor functions like gait performance and rotarod	[67]
QA Rat	Sprague Dawley and Fischer	Mimicking of striatal histopathology of HD	MSC	Improvement of cognitive function Improvement of spatial working memory	[74,76,77]
			Mouse ESC derived NSC	Reduction of striatal lesion Reduction of inflammation Prevention of loss of MSNs	
3NP-lesioned rats	All species except Fischer	Impairment of mitochondrial function resulting in cell death	MSC	Improvement of motor function Reduced striatal lesions	[78,79,80]
			NSC derived from human fetus	Reduced striatal lesions Reduction of inflammation Prevention of loss of MSNs	

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.

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.

Funding/support

This study was not funded.

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.

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