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Stem Cells Applications in Neurodegenerative Diseases

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Abstract

Neurodegenerative diseases are a kind of diseases caused by progressive loss of neuronal structure and function and glial cell homeostasis imbalance, there are many kinds of neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD); Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). So far, due to the lack of ideal treatment methods, it seriously threats to human health especially the elder population. Recently, with the rapid development of regenerative medicine, stem cells rely on their advantages including self-renewing capability, low immunogenicity, migration and homing capabilities, and stem cell derivatives including stem cells derived extracellular vesicles and stem cell-derived organoids, it provides unlimited application possibilities for the treatment of neurodegenerative diseases. In this review, we will summarize the recent research progress on the preclinical and clinical applications of stem cells in neurodegenerative diseases, hope that the reviews may provide some useful clues for researchers.

Keywords: Stem Cells; Parkinson's Disease; Preclinical Application; Clinical Application; Neurodegenerative Diseases

Abbreviations: BMMSCS: Bone Marrow Mesenchymal Stem Cells; PD: Parkinson Disease; HNSCS: Human Neural Stem Cells; AD: Alzheimer Disease; HIPSC: Human Induced Pluripotent Stem Cells; HD: Huntington's Disease; HESCS: Human Embryonal Stem Cells; HIDPSC: Human Immature Dental Pulp Stem Cells; ALS: Amyotrophic Lateral Sclerosis; ADSCS: Adipose-Derived Stem Cells.

Introduction

It is reported that there are 164.5 million Chinese citizens aged above 60 years old and 26 million elderly people aged above 80 years old in China in 2019, the proportion of the elderly population will increase to 26% of the total population by 2050; and the number of neurodegenerative diseases has correspondingly increased with the severity of global aging [1]; statistical results demonstrated there was 50 million people with dementia in the world, and the number will be increase to 150 million, in fact, 50–70% people with dementia will deteriorate to AD [2]; Shige Qi, et al. investigated and predicted that The prevalence of PD in China was 1.37% in the elderly population aged above 60 years old, this indicated that there will be 3.62 million PD patients in China [3]. Those data demonstrated that because lack of the effective treatment, the medical burden and economic burden of neurodegenerative diseases is on the rise globally.

Neurodegenerative diseases are a kind of disease in which nerve cells or nerve related cells are damaged, usually, nerve cells are almost unable to regenerate in adult, this undoubtedly increases the difficulty to cure for

neurodegenerative diseases. Stem cell technology as one of the greatest inventions of the 21st century, because its superior advantages including neural differentiation ability [4], migration and homing capabilities [5], and secreting the many kinds of neurotrophic factors [6], stem cells are becoming an ideal treatment method for neurodegenerative diseases. Here, we summarized the recent progress on the preclinical applications and clinic applications of stem cells in the neurodegenerative diseases, discuss the existing the problems and challenges in applications, which may provide some ideas for the further study of stem cells in neurodegenerative diseases.

The Preclinical Applications of Stem Cells in Neurodegenerative Diseases

Because of the diversity of stem cell types, the diversity of neurodegenerative diseases, diversity of animal models, and the diversity of administration methods, there are many preclinical applications of stem cells in neurodegenerative diseases have been reported in the past twenty years. Those evidences demonstrated no matter pluripotent or unipotent stem cells exhibit good therapeutic advantages in neurodegenerative diseases. The following table was a simple summary we collected for preclinical applications of stem cells in neurodegenerative diseases.

Cell Lines	Types Of Animal Models	Animals	Types Of Neuro degenerative Diseases	Administration Methods	Effects	The Underlying Mechanism	Refe-rences
BMMSCs	6-hydroxydopamine (6-OHDA) PD model	nine-week-old Wistar Han male rats	PD	surgical administration	Improve 6-OHDA PD motor and histological deficits	secreted several kinds of factors	[7]
hNSCs	APP/PS1 transgenic mice	/	AD	intranasal Transplantation	Improve neuroinflammation, cholinergic dysfunction, and pericytic and synaptic loss, and enhance adult hippocampal neurogenesis	hNSCs differentiated into cholinergic neurons,and secrete a variety of neurotrophic factors	[8]
human neural crest-derived nasal turbinate stem cells, human bone marrow MSCs	5×FAD transgenic mouse model of AD	16 weeks, male mice	AD	Injection administration	Reduce the Aβ plaque deposition and Aβ levels; regulate inflammatory microglial status; improve the cognitive impairment; increase neuronal survival	differentiated into neuron; modulation of autophagy	[9]
human NSCs	The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced C57BL/6 PD mice	C57BL/6 mice	PD	nasally administered	hNSCs were mainly distributed in the striatum, cortex, and hippocampus	/	[10]
hiPSC	6-hydroxydopamine (6-OHDA) PD model	RAG2 KO mice	PD	Injection administration	Long-Term Functional Motor Recovery;Reconstruction of the Nigrostriatal Pathway and Innervation of the Striatum	differentiated into mDA neurons	[11]

hiPSC	6-OHDA-lesioned rats;MPTP-treated monkeys	Seven–eight-week-old male and female NOG mice	PD	Injection administration	Functional behavior improvement	differentiated into mDA neurons	[12]
hESCs	6-hydroxydopamine (6-OHDA) PD model	rats	PD	Injection administration	Functional behavior improvement	differentiated into mDA neurons	[13]
human immature dental pulp stem cells (hIDPSC)	3-nitropropionic acid (3-NP) HD model	8 weeks male Wistar rats	HD	intravenous transplantation	improve BDNF expression and DARPP32 and D2R expression	secreted neuroprotective factor	[14]
hESCs	Viral vector HD model	8 weeks female Sprague–Dawley rats	HD	Injection administration	Improve motor dysfunctions	differentiated into GABA neurons	[15]
hNSCs	HD fragment model R6/2 mice; Q140 Knockin Mice	/	HD	Bilateral intrastriatal injections	improved motor and late-stage cognitive impairment	differentiated into neural populations	[16]
BMSCs	lumbar portion of the spinal cord of SOD1G93A mice	9 or 14 weeks old SOD1G93A mice	ALS	Injection administration	had only a transitory effect	/	[17]
ADSCs	transgenic SOD1G93A mice	/	ALS	Injection administration	protects motor neurons and reduces glial activation	secretion of neuroprotective factors; release of pro-inflammatory mediators	[18]

Table 1: The summary of preclinical applications of stem cells in neurodegenerative diseases

The Clinical Applications of Stem Cells in Neurodegenerative Diseases

Many scientists have demonstrated the feasibility of stem cells in treatment of neurodegenerative diseases from multiple perspectives and mechanisms, and with the further research and the openness of policies in various countries, there are several preclinical applications research of stem cells in neurodegenerative diseases enter into the clinical research stage, and achieved good clinical results in the recent five years. For example, Jeffrey S. Schweitzer, et al. obtained the iPSCs from an idiopathic Parkinson's disease patient, and implanted autologous iPSCs derived midbrain dopaminergic neurons into an elderly man aged 69-year-old with a 10-year history of progressive idiopathic PD, found that the symptoms of the patient were improved after implantation for 18-24 months [19]. Cudkowicz ME, et al. [20] recruited nine Alzheimer's disease patients at mild-to-moderate stage and treated the patients by three repeated injections of hUCB-MSCs, the results of clinic and physiological and biochemical indexes found that the hUCB-MSCs application on AD patients at mild-to-moderate stage was safe and effective [20] and we summarized the clinical applications of stem cells in neurodegenerative diseases which have been published in pubmed in Table 2. The collected data demonstrated that the clinical applications of cell lines in neurodegenerative diseases were MSCs but not ESCs or iPS, the type neurodegenerative diseases was ALS but not PD or AD (Table 2).

Cell Lines	Types of Neuro degenerative Diseases	Country	Observation Period	Clinical Stage	Side Effects	References
MSC-neurotrophic factors	ALS	US	28 weeks	phase III clinical trial	did not reach statistical significance on the primary endpoint	[21]
bone marrow MSC	ALS	Israel	7-8 months	phase II clinical trial	Weakness, Fatigue, Headache	[22]
ADMSCs	SMA	Iran	24 months	phase I clinical trial	/	[23]
hUCB-MSCs	PD	Korea	36 months	phase I clinical trial	Fever, Nausea, Headache	[20]
hNSCs	ALS	Novara, Italy	60 months	phase I clinical trial	Pain	[24]
MSCs	MSA	US	12 months	phase I /II clinical trial	Urinary tract infection, Headache, pain	[25]
MSC-neurotrophic factors	ALS	US	6 months	phase II clinical trial	Headache, pain, Pyrexia, Arthralgia	[26]

Table 2: The summary of clinical applications of stem cells in neurodegenerative diseases.

The Application Limitations of Stem Cells in Neurodegenerative Diseases

Recently, the preclinical and clinic applications of stem cells in neurodegenerative diseases have make the great progress, and stem cells exhibit the huge advantages in treatment of neurodegenerative diseases.

But there are several problems should be considered:

1. The source of stem cells. Stem cells can be divided into ESCs, iPS, NSCs, BMMSCs, UCB-MSCs according to the different classification methods, how to accurately define and differentiate the many kinds of stem cells and how to define the quality standards for stem cells are very important for stem cells clinical application, obtaining a large number of consistent characteristics and consistent quality stem cells that meet clinical usage standards is the key to the clinical application of stem cells
2. The differentiation and induction stem cells. Currently, there are many kinds of differentiation methods of stem cells, how to make sure orderly and consistent induction efficiency and how to obtain highly consistent stem cell derived functional neural cells, it is also a problem should be solved
3. The tumorigenicity of ESCs or iPS. Many articles have reported that ESCs or iPS could result in tumorigenicity because the pluripotency of ESCs or iPS, and it also become a huge obstacle for ESCs or iPS applications
4. Animal models of neurodegenerative diseases. The establishment of animal models is to maximize the simulation of human diseases, in fact, there is a significant gap in the existing animal models of neurodegenerative diseases in humans, this is also a huge obstacle for stem cells applications in neurodegenerative diseases
5. Formulation and update of policies and relevant laws and regulations related to stem cells. So far, stem cell related laws and regulations are also big obstacle for stem cells applications. For example, many European and American countries have established policies that prohibit stem cell related research, greatly limiting the applications of stem cells.

Conclusion

Although there are still many significant shortcomings in the basic research, preclinical and clinic applications of stem cells, with the research progress of regenerative medicine, the stem cells applications in neurodegenerative diseases will achieve great success in the future.

Competing Interests

The authors declare to have no conflicts of interest.

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