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Application of Induced Pluripotent Stem Cells in Alzheimer's Disease and Huntington's Disease

Jiaying Chi[1,a,*]

[1]*Universiti Tunku Abdul Rahman, Kuala Lumpur, 43000, Malaysia*
a. 17835207335@163.com
**corresponding author*

Abstract: Neurodegenerative diseases are characterized by the progressive loss of neurons or their myelin sheaths, leading to dysfunction and worsening over time. In Alzheimer's disease (AD) and Huntington's disease (HD), certain specific types of neurons are symmetrically lost in the patient's brain, and these specific neuron losses cause motor, sensory, or conscious disorders of the patient. Induced pluripotent stem cells (iPSCs) are multipotent stem cells obtained through reprogramming of somatic cells. The iPSC of patient origin carries disease-related genetic and epigenetic information, and its differentiation process can reflect the development of the disease to a certain extent. This makes iPSCs an ideal tool for building a variety of disease models, including AD and HD, offering valuable insights into disease mechanisms and potential therapeutic strategies. Since most AD and HD still lack effective treatment methods, clarifying the possible pathogenesis of AD and HD will become a prerequisite and foundation for effective prevention and development of the disease and finding effective treatment methods, which is of great theoretical and practical significance for improving the quality of life and longevity of the elderly.

Keywords: Neurodegenerative diseases, Alzheimer's disease, Huntington's disease, Induced pluripotent stem cells

1. Introduction

Human neurodegenerative diseases are a series of diseases characterized by the gradual loss of specific neuronal groups, leading to severe dysfunction and eventual death [1]. They can be classified as acute neurodegenerative diseases and chronic neurodegenerative diseases [2]. The latter include Alzheimer's disease (AD) and Huntington's disease (HD), which usually manifest later in life, involving the gradual degeneration of neurons, followed by a ruthless process that leads to the death of patients. Neurodegenerative diseases are often classified based on clinical, neuropathological, and possibly etiological factors, contributing to the understanding of their underlying mechanisms and potential treatment strategies. Neurodegenerative diseases such as AD and HD are not only devastating patients but also impose a significant burden on families and healthcare systems worldwide [3]. Among individuals over 65 years old, the prevalence of AD is about 30%. HD is a late neurodegenerative genetic disease, generally affecting people 30-50 years old, and they die 15-20 years after onset. As diseases that are difficult to treat and prevent, AD and HD have had a negative impact on the health and life well-being of the elderly, which has seriously affected the lives and safety of the elderly and has also had a series of adverse effects on the economic development of the

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whole family and society. Therefore, reducing the prevalence of AD and HD has become an urgent problem for researchers in the 21st century. So far, there is no specific drug that can stop the pathological process of AD and HD. The main reason is that the pathological mechanism of the disease is still unclear. The emergence of induced pluripotent stem cell (iPS)cell technology brings new opportunities to study the pathogenesis and treatment of AD and HD.

This article aims to explore the application of induced pluripotent stem cells (iPSC) in the study and treatment of AD and HD. By evaluating the advantages and limitations of iPSCs as a potential treatment method, this paper seeks to provide a new perspective for the treatment of neuroregressive diseases [4]. The research aims to enhance our understanding of the pathogenesis of AD and HD and proposes novel avenues for improving the quality of life and longevity of the elderly through the reprogramming of somatic cells through gene transfection technology [5, 6].

2. The Common Pathogenesis of Alzheimer's Disease and Huntington's Disease

Studies have shown that the wrong folding and aggregation of proteins are common features in numerous neurodegenerative diseases. The wrong folding of proteins can affect the normal functioning of their biological functions and even produce harmful oligomers, which is closely related to the binding of molecular partners and proteases during intracellular translation. Protein aggregation begins with the appearance of an agglomeration nucleus. Once nucleated, the protein monomer with a tendency to gather in the cell randomly folds to produce a misfolded and inoperative protein polymer, and the oligomers further converge to form a fibrous aggregate. Oligomers and polymers can be degraded by a variety of protein molecular partners through ubiquitin-proteasomes or autophagy; failed degradation of oligomers and polymers can produce cytotoxicity, causing cell death and inflammation [1]. Neurodegenerative diseases, including AD and HD, are related to the polymerization and deposition of proteins that are misfolded, such as amyloid plaques and nerve fibers in the brain of AD patients and Huntingtin (HTT) protein in HD [1].

Despite the central role of protein aggregation in these diseases, drugs aimed at removing amyloid plaques or protein polymers have not significantly improved the progression of the disease or the decline of cognitive function. This highlights the need for further research to identify alternative therapeutic targets.

3. Alzheimer's Disease

3.1. Pathological Changes and Pathogenesis of Alzheimer's Disease

AD is a common neurodegenerative disorder in elderly groups, characterized primarily by memory and learning dysfunction, and accounts for about 80% of dementia cases [1]. In 2020, China's elderly population aged 65 and above will reach 191 million, the aging rate will reach 14% in 2022, and it is predicted that it will reach 20% around 2030 [7].The hallmark pathological changes in the brains of AD patients include obvious brain atrophy and shrinking, particularly in the hippocampus, amygdala, olfactory cortex, and neocortex. At the microscopic level, pathological changes in the AD brain are senile plaques formed by extracellular amyloid aggregation and nerve fiber entanglement formed by intracellular excessive phosphorylated Tau protein aggregation, as well as the loss of neurons and synapses [8].

The pathogenesis of AD is multifactorial, with several hypotheses proposed to explain its onset and pathogenesis. They all try to understand and explain the pathogenesis and pathological process of AD from a certain point, but the pathogenesis of AD is still unclear. P-amyloid protein (AP) cascade theory holds that the core link of AD is AP, and the abnormal secretion and production of AP are the causes of other relevant pathological changes. AP is a P-amyloid polypeptide produced by APP under the action of P- and Y-secreting enzymes. Presenilin proteins (PS-1 and PS-2), the

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main components of secretory enzymes, are also the "culprits" of AD. Excessive deposition of soluble AP fragments can induce neurotoxic cascade reactions, further cause excessive phosphorylation of Tau protein and loss of neurons, and eventually neurodegenerative lesions. Therefore, AP has always been regarded as the most potential therapeutic target. However, the failure of many drug research and development projects based on the AP cascade hypothesis has forced people to re-examine the authenticity of the AP cascade hypothesis. The research on drugs for the treatment of Alzheimer's disease has four main categories according to the mechanism of action: cholinesterase inhibitors, non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonists, and drugs that act on AP and Tau proteins. Only drugs with cholinesterase inhibitors and NMDA receptor antagonists are approved for the clinical treatment of AD. These approved drugs are also only focused on improving symptoms and cannot delay or cure the disease. Many potential compounds have a very good improvement effect on preclinical AD animal models, but once they are applied in clinical practice, they have to face the fate of failure. The reason is the lack of a model that can truly and objectively reflect the characteristics of human diseases [8].

3.2. Application of Induced Pluripotent Stem Cells in the Treatment of Alzheimer's Disease

Induced pluripotent stem cells use mouse fibroblasts to induce induced stem cells similar to embryonic stem cells. The expression of the Fbx15 factor can be used to detect the pluripotency of newly induced cells, and clones expressing Fbx15 factors can be produced as long as the cells jointly express Oct4, Sox2, Klf4, and C-myc [9].

For diseases with neurodegenerative changes such as AD, the advantages of inducing pluripotent stem cells are that they are stable, will not produce immune rejection, and will not produce moral and ethical problems such as damaging human embryos and cloning humans. Therefore, inducing pluripotent stem cells can replace other cell transplantation to treat AD. Because of the high expression of the main regulatory factor of embryos, neurosox2, neural stem cells and meningeal cells are more likely to be induced to be induced pluripotent stem cells, because the acquisition of neural stem cells is very limited, and the induction of pluripotent stem cells induced by meningeal cells is more suitable for the cell transplantation treatment of AD [10]. The development of human-induced pluripotent stem cell research will provide more effective treatment measures for neurodegenerative diseases such as AD. iPSCs are similar to embryonic stem cells in terms of morphology, gene and protein expression, epigenetic modification state, embryo-like and deformed tumor generation ability, and differentiation ability. The patient's somatic cell reprogrammed iPSCs carry the patient's genetic material, and the disease-related cells produced by differentiation also contain genetic modification and mutations that play an important role in the occurrence of the disease, which have been used in disease model construction, potential mechanism research and drug screening [8]. However, before it is really applied to clinical treatment, there are still many problems that have not been solved: For example, the mechanism of inducing somatic cell reprogramming to induce pluripotent stem cells is still unclear; it is unknown whether the induced differentiation of induced pluripotent stem cells is the same as the induction conditions of embryonic stem cells. The number of induced pluripotent stem cells required for treatment and how to grasp the amount of cells are also problems that need to be solved. Therefore, scientists are also looking for ways to optimize the establishment of iPSCs, improve the efficiency of iPSC preparation, and establish efficient, safe, and practical methods.

4. Huntington's Disease

4.1. Research on the Pathogenesis of Huntington's Disease

Huntington's disease (HD) usually manifests in individuals between the ages of 30 and 40, with early symptoms including involuntary dance-like movements, cognitive impairment, and mental

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abnormalities. HD is caused by the repeated amplification of the CAG trinucleotide sequence at the 5' end of the Huntington gene 1 of the Huntington gene encoded by the Huntington protein chromosome 4. Among them, the number of repetitions of wild type is generally less than 35. When the number of repetitions reaches more than 36, the structure of Huntington protein will change. When the number of repetitions is 40 or more, there must be Huntington patients. However, the number of CAG repetitions between 36 and 39 is not completely dominant [5]. At present, there are two speculations: first, there is a modulator upstream of the it-15 gene that controls the length of the CAG repeat sequence; the other is that there is a repair enzyme similar to telomerase in the organism, which can synthesize the CAG repeat sequence according to its own sequence [11]. However, these speculations have not been confirmed. Huntington's disease is an autosomal dominant neurodegenerative disease. The study of iPS technology on Huntington's disease is a good disease model. The protein expression map of iPSCs in patients with Huntington's disease is different from that of iPSCs in normal people, which is consistent with known changes in the function of Huntington's disease cells. In addition, the expression map of cell genes and proteins with shorter CAG amplification is more likely to be disturbed than the expression map of genes and proteins with longer amplification. Differentiated Huntington's disease nerve cells show disease-related phenotypes, including changes in electrophysiology, metabolism, cell adhesion and cytotoxicity. The cells with the longest expansion are the most vulnerable to cellular stressors, including the withdrawal of nutrients from the cell culture medium, especially the absence of BDNF, which once again confirms the dependence of patients with Huntington's disease on repeated growth [11, 12].

4.2. Therapeutic Application of Induced Pluripotent Stem Cells in Huntington's Disease

Perhaps the most direct benefit of iPSC technology is the development of disease modeling and small molecular treatment solutions. In order to explore the pathogenesis of Huntington's disease and cell substitution therapy, non-viral and non-gene integration cell reprogramming and new gene editing technology to correct patients' specific iPS genes have broadened ideas for the research and treatment of diseases [4]. Cells need to use genome-wide sequencing or other methods to test whether they cause other mutations, staining weight formation or epigenetic changes. And cell culture should be carried out under good growth conditions, and a neuroprecursor and undifferentiated cells should be distinguished by appropriate methods to minimize the risk of teratoma occurrence and identification by the autoimmune system. There is a lot of early clinical work before cells are transmitted to the right area of the brain to ensure that cells are safely introduced into the brain without causing tumor occurrence and immune response, and then it needs to be proved that they can form functional connections. This is a difficult challenge, but at least in theory it may be achievable. The vast majority of treatments are still unknown. At present, a variety of drugs for HD are aimed at preventing the formation of aggregates and inclusions. Their efficacy is limited and may cause intermediate accumulation and aggravate diseases. However, reprogramming is possible for fewer cells to be affected by the pathogenic process. Further clarifying the pathogenesis of HD will help to open up new ideas for the treatment of HD and have a positive impact on the treatment of other neurodegenerative diseases, including HD [5].

5. Conclusion

Induced pluripotent stem cells (iPSCs) are a new type of cell with similar functions to embryonic stem cells found in recent studies. It provides a new vision for the treatment of neurodegenerative diseases such as Alzheimer’s disease and Hungtington’s disease. These cells, derived from adult somatic cells, possess similar pluripotent properties to embryonic stem cells, enabling them to differentiate into various cell types, including neurons, which can potentially repair or replace

damaged tissues in the brain. The development of iPSC-based therapies has opened new avenues for treating AD and HD, disease that have long been characterized by complex pathogenesis and limited therapeutic options.

Research into their causes, pathogenesis, and treatment strategies has been ongoing for decades, yet effective treatments remain elusive. After the successful acquisition of human stem cells, the application of stem cells to treat AD and HD has become a new direction of treatment. Animal models of stem cells treating AD and HD have achieved remarkable effects. These models have demonstrated promising results in terms of ameliorating disease symptoms and promoting neuronal regeneration.

However, there are also many shortcomings in animal models. For example, most animal models use lower mammals such as mice or rats. However, compared with these, non-human primates are more than humans in genetics, anatomical structure and physiological functions. It is highly similar and is an ideal animal for AD and HD modeling. Therefore, on this basis, non-human primates should be used as animal models of AD and HD in order to accurately study the effectiveness of stem cell therapy.

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