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Current Research Status of Cerebral Degenerative Diseases: A Perspective from Traditional Chinese Medicine and Western Medicine

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Abstract. As the global population ages, neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) have become major health threats to the elderly, with currently limited treatment options available. This review focuses on the application of modern medical technologies—including CRISPR/Cas9 gene editing and neural stem cell-based therapies—and traditional Chinese medicine (TCM) therapies (i.e., interventions guided by TCM theory) in the treatment of neurodegenerative diseases. Employing a literature review methodology, this review explores key issues, such as the limitations of current treatment approaches and the potential of integrating Chinese and Western medicine. Research has found that CRISPR/Cas9 shows potential in HD models but faces significant delivery challenges. Neural stem cells can serve as transplant donors or gene carriers, yet they lack the ability to differentiate into specific cell types. Traditional Chinese medicine theories can alleviate symptoms through multiple pathways. This review integrates multidisciplinary technologies and theories to provide new directions for the prevention and treatment of neurodegenerative diseases.

Keywords: neurodegenerative diseases, CRISPR/Cas9, neural stem cells, Traditional Chinese Medicine, invigorating the kidney and generating marrow

1. Introduction

The global aging process is accelerating, with the incidence of neurodegenerative diseases (such as Alzheimer's disease, Parkinson's disease, and Huntington's disease) rising year by year. Such diseases cause progressive damage to brain tissue, impair cognitive and motor functions, and thus impose a heavy burden on families and society. Current treatment primarily focuses on symptom management, as the underlying mechanisms remain incompletely understood. Recent studies have shown [1] that CRISPR/Cas9 gene editing technology has demonstrated preliminary therapeutic efficacy in Huntington's disease mouse models [2]; Neural stem cells offer new avenues for nerve regeneration [3]; Traditional Chinese Medicine theories (kidney-bone marrow generation, spleen-stomach theory) demonstrate therapeutic effects on Alzheimer's disease and Parkinson's disease [4-6]; Diagnostic technologies such as the “Ikawa stimulation test” enable early disease detection [1]. However, CRISPR/Cas9 faces challenges such as low in vivo delivery efficiency; neural stem cells

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lack the ability to differentiate into specific cell types; and the mechanism of action of TCM in treating these diseases remains insufficiently elucidated [2-4]. This review employs a literature-based approach to synthesize the aforementioned advances, aiming to clarify the multidisciplinary application potential and provide theoretical support for clinical practice.

2. Advances in Western medical treatment technologies

Since its first report in 2012, CRISPR/Cas9 has been improved. It exhibits characteristics such as species universality, high efficiency, high throughput, and low cost, making it the most commonly used gene editing technology at this stage. It can be applied not only to isolated neuronal cells but also to fertilized eggs, embryos, and adult organisms, thereby achieving effects at the in vivo brain tissue level [2]

2.1. Application scenarios in degenerative brain diseases

Brain gene and function research: exploring the role of genes in brain function regulation through the editing of specific genes [2]

Disease modelling: facilitating the construction of knockout/knock-in mouse models (e.g., HD140Q knock-in mice) and providing tools for the study of disease mechanisms [2]

HD140Q knock-in mice: Construction Principle Based on CRISPR/Cas9 Gene Editing Technology: The CRISPR/Cas9 system consists of Cas9 nuclease and guide RNA (gRNA). The gRNA recognises and binds to a specific sequence of the target gene and directs Cas9 nuclease to cleave the DNA double strand at that site, causing a double strand break (DSB). The cell's own repair mechanism will repair the breaks, and during the repair process, if donor DNA containing a specific exogenous gene fragment (e.g. HD140Q gene, a fragment of the human Huntington's disease-causing gene containing 140 CAG repeats) is provided, the cell will integrate the exogenous gene into the genome either by homologous recombination or non-homologous end joining, thus achieving knock-in and enabling the mouse to acquire the specific gene modification [2].

HD140Q knock-in mouse construction: In the construction of HD140Q knock-in mice, gRNAs targeting specific regions of the mouse Huntington gene are designed to direct Cas9 nuclease to cleave this region. Meanwhile, a fragment of the human Huntington's disease-causing gene (i.e., the HD140Q gene)—which carries 140 CAG repeats—is introduced as an exogenous gene, along with Cas9 nuclease and gRNA, into mouse fertilized eggs or embryonic stem cells. The HD140Q gene is integrated into specific loci of the mouse Huntington gene via the cell's intrinsic repair mechanism. Subsequent screening and breeding yield a mouse model that stably carries the HD140Q gene [2].

Experimental treatment: CRISPR/Cas9-based experimental treatment has been applied to the HD mouse model (HD140Q knock-in mice), showing encouraging efficacy and initially demonstrating good therapeutic potential [2]

2.2. Technology implementation methodology

2.2.1. Common methods of implementation

Adeno-associated virus (AAV) mixtures are mostly used for CRISPR/Cas9 gene editing in the brain of adult mice. AAV is an envelope-less, single-stranded, DNA-deficient virus that infects both dividing and non-dividing cells and is usually non-pathogenic, making it an important vector for in vivo delivery of this technology [2].

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Issues related to delivery vectors (commonly used method of intracerebral editing in adult mice is injection of adeno-associated virus AAV mixtures, which are unenveloped, single-stranded, DNA-deficient, infect both dividing and non-dividing cells, and are generally non-pathogenic, but have limitations)- Differences in editing efficiency in brain regions: after injection of AAV into the mouse hippocampus, gene editing was easily achieved in the dentate gyrus, while efficient editing of neuronal cytosol in the CA1 region was more difficult [2].

Loading capacity limitation: classical Streptococcus pyogenes Cas9 enzyme (SpCas9) in combination with the MECP2 promoter requires that SpCas9 be packaged separately from the gRNA. Alternatives such as Staphylococcus aureus SaCas9 enzyme (small volume), integrase-deficient lentivirus (large volume), but both have limitations [2].

Low editing efficiency: Currently, the overall efficiency of neuronal gene editing in the brain is low, and even with the modified homology-independent targeted embedding (HITI) method of the Belmonte lab of the Salk Institute, the actual editing efficiency is significantly lower than 5% as the intracerebral injections of the mice only yielded data from the visual cortex [2].

Experimenting with neuron-specific novel small promoters, preliminary packaging of SpCas9 with a gRNA single AAV vector has been achieved; We plan to subsequently validate the in vivo application of the highly efficient viral vector AAV-PHP.B to enhance the efficiency of neuronal editing in the brain

Efficient and safe in vivo delivery (in vivo) of CRISPR/Cas9 is still a challenge that needs to be broken through [2]

2.2.2. Neural stem cell therapy

Cell transplantation therapy: neural stem/progenitor cells can be isolated from the developing or adult CNS and cultured in vitro into immortalised cell lines (myc, SV40, large T antigen and other oncoproteins are commonly used for immortalisation); Transplantation into brain regions of Parkinson's disease and Alzheimer's disease models, e.g. human neural progenitor cells induced by EGF and bFGF were transplanted into the striatum of rats with Parkinson's disease, and after 20 weeks, they could be differentiated into tyrosine hydroxylase-expressing neurons, which partially improved the movement disorders; Grafted cells no longer proliferate after removal of mitogen signalling and are not tumourigenic [3]

Gene therapy vectors: immortalised neural progenitor cell lines can be used as vectors for the transfer of exogenous genes (e.g. E. coli β-galactosidase, neurotrophic factor NGF, transmitter synthetase tyrosine hydroxylase TH, metabolising enzyme β-glucosidase, etc.); ; For example, NGF-secreting cell line constructed from HiB5 immortalised cell line can express NGF for more than 10 weeks when implanted into the brain, and promote the growth of cholinergic neurons; Stem cell transplants carrying the TH gene, glial cell-derived neurotrophic factor GDNF gene, enable gene expression and protect nigrostriatal cells in Parkinson's disease models [3]

Difficulty in inducing neural stem cells to specifically and completely differentiate into specific types of neurons, limiting their precision therapeutic applications [3]

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3. Study on the intervention of cerebral degenerative diseases under the guidance of traditional chinese medicine theory

3.1. Application of the theory of 'kidney generates marrow'

Cognition of core pathomechanism: Based on the theories of "the kidney generates marrow" and "the brain is the sea of marrow", it is believed that the fundamental pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), and other cerebral degenerative diseases is deficiency of kidney essence, which leads to emptiness of the brain marrow. The core clinical manifestations of these diseases are consistent with the TCM syndrome of "kidney deficiency and marrow emptiness" [5-7]. The basic symptoms are the same as 'kidney deficiency and empty marrow' [5-6]

Therapeutic principles and mechanisms: The fundamental therapeutic principle of "invigorating the kidney and replenishing the marrow" is consistent with the TCM concept of "treating different diseases with the same therapy based on similar syndromes". The structure and function of neurons are regulated by the excitatory neurotransmitter glutamate and the inhibitory neurotransmitter γ-aminobutyric acid (GABA). The TCM strategy of "invigorating the kidney to replenish the marrow" may exert effects by regulating neurotransmitter balance and inhibiting neuronal apoptosis [5-6].

3.2. Application of the spleen and stomach doctrine

The spleen and stomach are the basis of vital energy: The Yellow Emperor's Inner Canon (Huangdi Neijing) states that "the spleen and stomach are the officials in charge of the granary, from which the five flavors (sour, bitter, sweet, pungent, salty) originate". It also notes that the spleen and stomach are responsible for the transportation and transformation of water and grain, which generates essence and nourishes qi [4]. The Treatise on the Spleen and Stomach emphasises that 'vital energy is the essence of the innate, and it cannot be nourished without the stomach qi', and that normal functioning of the spleen and stomach is the key to sufficient vital energy, which enhances the body's ability to resist disease, and that damage to the spleen and stomach is prone to positive deficiencies and evils [4]

The spleen and stomach are the pivot of gasification: 'Su Wen, six micrography', 'lifting and lowering of the interest of the gas stand alone', the spleen and stomach are the core of the qi of the internal organs, the spleen rises and the stomach descends to maintain the qi movement and safeguard the activities of life; From the perspective of the five zang organs (heart, lung, spleen, liver, kidney), it is recorded that "the heart and lung govern exhalation, the kidney and liver govern inhalation, and the spleen absorbs the essence of grain during the interval between exhalation and inhalation". From the perspective of yin-yang and five elements theory, it is stated that "yin and yang, together with water and fire, reside in the upper and lower parts of the body, while earth (corresponding to the spleen and stomach in TCM) resides in the middle. The upper and lower parts must interact with each other, and this interaction relies on the middle earth (spleen and stomach)" [4].

Direct connection between the spleen and the brain: the spleen acts on the brain through 'God', "blood" and 'fluids' -- the spleen hides the mind and is the master of thought The Spleen is involved in the regulation of the Yuan Shen; The spleen is responsible for the ascending and clearing of blood, governing blood (preventing abnormal bleeding), and transporting the essence of qi and blood upwards to nourish the brain [4]. Spleen dysfunction generates phlegm-dampness, which obscures the clear orifices and leads to loss of cerebral and mental nourishment; The stomach is connected to the brain through the meridian qi ('Ling Shu, Movements and Transmissions',

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'Stomach qi is injected upwards into the lungs, and its humourous qi rushes upwards to the head, goes through the pharynx upwards to the empty orifices, and then through the eye system, and enters the cerebrum') and the grains and juices are received by the stomach and nourished by the medulla oblongata, thus providing a material basis for the generation of the brain and the mind [4]

The Role of the Spleen and Stomach Doctrine in Disease Intervention:For Alzheimer's disease and Parkinson's disease, weakness of the spleen and stomach is the key to the pathology -- spleen deficiency can generate phlegm and cause blood stasis, and the combination of phlegm and blood stasis will aggravate the brain damage; By regulating the spleen and stomach, it can improve the transport of water and grains, enhance the production of qi and blood, and reduce pathological products such as phlegm-dampness and blood stasis, thus protecting brain function and delaying the progression of the disease [4]

4. New advances in diagnostic techniques for degenerative brain diseases

4.1. Breakthrough value of the 'Igawa-inspired experiment'

The 'Igawa-inspired experiment' was developed based on the theory that "insufficient growth hormone secretion is the primary cause of aging and central nervous system (CNS) degeneration". It works by observing patients' ability to secrete growth factors in response to specific chemical stimuli, thereby reflecting the secretion status of neuromediators in the CNS [1].

Accurate differential diagnosis: It can effectively differentiate between Alzheimer's disease (AD), senile dementia, and the normal aging process. Specifically, AD patients show almost no response to the stimulation test, while the responses of senile dementia patients and individuals with normal aging differ significantly in terms of magnitude and temporal distribution; Only some of the cases of progeria diagnosed by traditional methods (MRI, positron emission scanning, electroencephalography) are 'true progeria', and the test improves the diagnostic accuracy [1]

Guidance for individualised treatment: the amount and manner of growth factors required for the treatment of progeria and Alzheimer's disease are different, and the test can reflect the rhythms of cellular biochemical and biophysical activity, providing a basis for the development of a treatment plan that guarantees efficacy and specificity [1]

Enabling early intervention: Early diagnosis of senile dementia can be achieved, and early treatment can promote the recovery of patients' body functions and improve their prognosis [1]

4.2. Limitations of traditional diagnostic techniques

Imaging examinations such as nuclear magnetic resonance and positron emission scanning, although capable of observing structural changes in the brain (e.g., cerebral atrophy), are not sensitive enough to identify subtle pathological changes in the early stages of the disease, making it difficult to meet the demand for early diagnosis; electroencephalograms, which mainly reflect the electrical activity of the brain, have a limited diagnostic value in the specific diagnosis of cerebral degenerative diseases [1].

5. Conclusion

Current research on cerebral degenerative diseases faces challenges from both bottlenecks in modern medical technologies and limitations in the clinical application of traditional Chinese medicine (TCM). The former include the need to enhance the in vivo delivery efficiency and safety of CRISPR/Cas9, the incomplete elucidation of the mechanisms underlying the induction of neural

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stem cell-specific differentiation, and the inability of existing drugs to reverse disease progression [2-3].The latter are reflected in the insufficient explanation of the modern scientific mechanisms underlying TCM-related theories, the lack of standardised diagnostic classification and efficacy evaluation systems, and the need to improve the standardisation of clinical application protocols [4-6].

In view of the current challenges in the research of degenerative brain diseases, future breakthroughs can be made in the optimisation of technology, the integration of Chinese and Western medicine, and the improvement of diagnostic system, i.e., improving CRISPR/Cas9 delivery vector and exploring the targets of neural stem cell differentiation and regulation [2-3], combining Chinese medicine and modern medical cognition to build a synergistic therapeutic plan, validating the value of "Yachikawa stimulation test 'We have established a multi-dimensional early diagnostic system of ’functional assessment + structural imaging + molecular markers" by combining biomarkers [1].

The research of degenerative brain diseases should not only cope with the existing challenges of modern medical technology (e.g. gene editing, stem cell research) and the application of traditional Chinese medicine, but also promote the enhancement of disease diagnosis and treatment and clinical translation of the research results through the optimisation of technology, the integration of traditional Chinese and Western medicine, and the improvement of diagnostic system in the future.

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