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The Current Treatment for Neurodegenerative Diseases

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Abstract. Neurodegenerative diseases (NDs) refer to dysfunction of central nerve system, characterized by progressive loss of neuronal structure and function, ultimately resulting in decline in patients' memory, motor ability, language and intelligence. The typical NDs include age related diseases like Aleimer's disease (AD) and genetic diseases such as Huntington's diseases (HD) and amyotrophic lateral sclerosis (ALS). NDs impose heavy economic burden and suffer to the enormous patients over the world, however, many types of NDs do not have a cure; existing treatments only aim to improve their symptoms. Under that condition, Gene therapy has shown potential for transporting some genetic products into the cells and correct faulty genes. Over the years, research have highlighted the promise of gene therapies using AAV vector in treating NDs. At the same time, a number of emerging therapeutic technologies for neurodegenerative diseases, such as epigenetic interventions through acetylation/deacetylation, gene therapies that target specific mRNAs or non-coding RNAs, and photo biomodulation therapies that can act on brain tissue, are also being studied. In this discussion, we explore the historical, present, and future outlook of gene therapies for neurodegenerative conditions.

Keywords: Neurodegenerative disease, treatment, CAR-T, AAV.

1. Introduction

Neurodegenerative diseases are kinds of diseases that are caused by gradual loss of normal nerve function. Patients' nerve systems are gradually damaged, and they may have different symptoms due to the different regions of the damaged nerve system. NDs include a range of diseases and some typical cases are AD, HD, PD. These diseases may have some different risk factors, but they all can lead to the motor or mental challenge to patients. NDs have become more prevalent in 21st century, as the elder population increase. Taking the example of Alzheimer's disease, its disease rate is 3.9% among adults aged 60 or elder in China [1]. And the population of people over 60 years old is about 300million in China, so the elder patients of Alzheimer's disease is about 11.7million. Using the same method, approximately 50 million dementia patients are estimated worldwide.

NDs presents a significant challenge in the world not only because of the large number of patients affected but also because NDs impose heavy burdens on individuals, families, and healthcare systems globally. Therefore, finding treatment methods for NDs is extremely urgent.

At present, NDs still lack effective clinical treatments, and their pathogenic mechanisms remain to be elucidated [2]. Although the exact cause of each neurodegenerative disorder may differ, a shared characteristic among them is the occurrence of neuroinflammation, which is a persistent and uncontrolled immune reaction within the central nervous system [2]. This complexity presents challenges in finding treatments for NDs. Over the past few years, there has been an increasing emphasis

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on the impact of neuroinflammation on the progression of NDs. Studies have revealed that inflammation in the nerve system can create some reactive oxygen species, which play a role in the progression of NDs [1]. Microglia and astrocytes are two kinds of neuroglial cells found in the brain. They have been identified as key players in the process of neuroinflammation, releasing inflammatory cytokines that contribute to neuronal damage. Other kinds of pro-inflammation materials are the deficit proteins such as Aβ protein in the AD and α-synuclein in the PD. the build-up of these proteins can initiate and perpetuate neuroinflammatory responses. Conventional NDs' treatments have primarily concentrated on providing relief from symptoms, but they have little effects in delaying or stopping the progression of the diseases. The above conditions have shown the complexity of treating NDs, and the restrictive properties of the cerebrospinal barrier has made the drug development process of NDs more challenging. Nevertheless, recent progress in gene therapy provides hopeful prospects for addressing neuroinflammation and NDs.

This article seeks to investigate the most recent developments in gene therapy approaches that focus on treatments of NDs. Gene therapy has become a rapidly growing field in biology and medical researches. It has the ability to regulate the immune response, restore or substitute impaired neurons, and reduce the harmful effects of misfolded proteins. Through targeting the root causes of neurodegeneration, gene-based treatments provide a promising outlook for enhancing the well-being and decelerating the advancement of the disease in impacted patients [3].

2. Therapy of NDs

In recent years, researchers have demonstrated that adaptive immune cells are essential for the regulation of brain function [4]. Under that condition, immune cell therapy may offer a solution as it is capable of managing the current immune response and eventually alleviate the symptoms of neurodegenerative disorders.

2.1. CAR-T therapy in NDs

CAR-T (Chimeric antigen receptor T-cell immunotherapy) is an emerging cellular immunotherapy for combating blood cancers. CAR molecules are chimeric receptors located on the surface of cells, along with a CD3 signaling domain. When antigens are detected, these receptors on the T cells activate TCR signaling pathways downstream such as NF-κB, MAPK and PI3K/AKT. These downstream pathways can alter the expression of specific gene and eventually lead to excretion of cytokine and proliferation of CAR-T cells. The activated CAR-T cells can exercise a range of functions such as killing abnormal cells and regulating immune response depending on the kind of T cells activated.

CD8+ T cells equipped with CARs that target tumor-specific antigens or neoantigens have demonstrated promising results in fighting specific hematological cancers by targeting cell-surface proteins like CD1 that are commonly found on tumor cells [5]. After that, it is possible to direct the cytotoxic activity of these cells to eliminate tumor cells by releasing particles like granzymes, perforins and cytokines. When it comes to the NDs, the CAR-T therapy is different from that of the cancer. Unlike incorporating CAR molecule into CD8+ T cells, it is proposed to equip CD4+ T cells with CAR molecule, because CD4+ CAR-T cells are anticipated to have a positive impact by modulating neuroinflammation via the release of beneficial cytokines and coordinating the innate immune response. Besides some recent researches have shown that CAR-T cells can be utilized in addressing specific inflammatory and autoimmune disorders, including viral infections and mouse model of autoimmune encephalomyelitis [5]. This is achieved by incorporating CAR molecules into Treg cells to inhibit harmful immune reactions.

Those researches discussion above bring new insight for using CAR-T therapy in NDs. The cellular immunotherapy could potentially provide a promising opportunity to target the underlying reasons for NDs with specificity and efficiency.

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2.2. AAV therapy in NDs

Adeno-associated virus (AAV) therapy, which is a kind of gene therapy. Gene therapy normally means delivering genetic material (DNA or RNA) into human cells to alter genes, aiming to prevent and treat diseases. Gene therapy can work through various approaches, such as replacing mutated disease-causing genes with functional ones, suppressing disease-causing genes, or introducing a new gene to aid in disease treatment.

The keys of gene therapy are specificity, efficiency and safety of the gene delivering process. Gene transfer carriers encompass viral vectors as well as non-viral vectors. Non-viral vectors commonly comprise of either bare plasmid DNA or DNA combined with lipids to create nanoparticles. Non-viral delivery often results in only transient gene expression, making it less suitable for neurodegenerative diseases. Various categories of viral vectors exist [6]. Among these, AAV vectors are the most widely used and considered the most promising gene delivery vehicles. It has become the main vector used in clinical trial of treating central nerve system diseases. After decades of development, AAV gene therapy has achieved a series of inspiring successes.

AAV gene therapy is a treatment method where therapeutic genes are delivered into the patient's body using recombinant AAV viruses as vectors. AAV, a member of the Parvoviridae family, is a virus with a single-stranded DNA structure. AAV viruses lack an envelope and consist of a 25 nm diameter icosahedral protein capsid and a single-stranded DNA genome of approximately 4.7 kb. Each end of the genome contains inverted terminal repeats (ITRs), and the middle section includes three open reading frames encoding Rep, Cap, and AAP [7].

The ability of AAV vectors to mediate long-term stable transgene expression is one of the key reasons why AAV gene therapy is particularly suitable for treating Alzheimer's disease (AD). Many gene therapies for CNS diseases require sustained transgene expression throughout the entire lifespan. When AAV infects host cells, it first binds to AAV receptors on the cell surface, then enters the cell through endocytosis mediated by grid proteins. In the cytoplasm, AAV is transported via vesicles into the cell nucleus. Once in the nucleus, the AAV capsid disintegrates, and the AAV genome undergoes either intermolecular or intramolecular recombination driven by ITRs, forming episomal forms that can persist in the nucleus. Therefore, although the integration of the AAV genome into the host genome is very low, the gene expression mediated by AAV is sustained and stable in non-dividing cells. Unlike peripheral organs, the majority of CNS cells affected by Alzheimer's disease (AD) are post-mitotic non-dividing cells. Therefore, AAV gene therapy may exert a sustained or even permanent therapeutic effect on AD. Compared to other viral vectors, AAV demonstrates greater stability in long-term gene expression. Injections performed 12 months prior still detect ApoE expression delivered by AAV in mouse brains, whereas adenovirus delivery of the same construct ceases expression after 6 weeks [8]. Studies have shown that AAV-AADC, following a single injection into the brain parenchyma of non-human primates, maintains AADC expression for over 15 years. Thus, following a single administration, AAV-mediated gene therapy offers long-term or even lifelong efficacy against CNS diseases, making it particularly attractive for treating AD.

As an emerging therapeutic approach, AAV gene therapy has achieved significant success in the treatment of monogenic rare diseases. After all, AAV gene therapy is still in its early stages of development, and its potent effects require further exploration and development. Continuous accumulation of experience and innovative treatment strategies are essential in clinical practice.

3. Preclinical study to clinical trial of some NDs

Neurodegenerative diseases are classified into many types, each with its own unique pathogenic mechanisms. Therefore, conducting preclinical mechanistic studies on individual types of NDs and clinical studies on different treatments is crucial. Now, we will have a deep look at some specific NDs.

AD is characterized by progressive memory loss and cognitive decline as typical clinical manifestations, along with emotional, personality, and behavioral abnormalities. Pathologically, AD is marked by extracellular β-amyloid (Aβ) plaques and intracellular phosphorylated tau protein tangles in brain tissue. AD lacks a definitive etiology, and its pathogenesis remains unclear. Currently, it is widely

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believed to be a multifactorial and complex disease involving multiple genes, various pathological mechanisms, and several environmental risk factors.

AD causes immense suffering for patients and their families, as well as imposing heavy economic burdens on families and society. So, it is crucial to find effective treatment drugs of AD. Currently, there are only four drugs used to treat AD, including three acetylcholinesterase inhibitors: Donepezil, Rivastigmine, and Galantamine; and one NMDA receptor antagonist: Memantine. These drugs target neurotransmitters and thus address the end-stage of the disease, providing symptomatic relief but not slowing the progression of the disease. Furthermore, almost all large molecule drugs and most of small molecule drugs cannot penetrate the blood-brain barrier, which limits the development of many CNS disease medications. All these factors have made the development of traditional central nervous system drugs very challenging, but in recent years, emerging gene therapies have changed this situation.

Numerous AAV gene therapy medications have received approval for clinical use in treating a range of conditions. Luxturna and Zolgensma are targeted for two kinds of neurodegenerative-related diseases including genetic retinal diseases and spinal muscular atrophy. Their successes suggest that AAV gene therapy may also make significant progress in treating other challenging neurodegenerative diseases like Alzheimer's disease (AD). Accordingly, AAV gene therapy for AD has garnered widespread attention, becoming a new area and direction for AD drug development.

Some preclinical trials demonstrated that AAV vector combined with Aβ protein antibody gene is proved to be an effective AD treatment. The prophylactic and therapeutic administration both significantly reduce Aβ levels in the brains of AD model mice [9]. Besides, it is reported that monoclonal antibody (mAb) designed to target amyloid beta (Aß) protein can be used to decrease the bulid-up of Aβ within the brains of human Aß transgenic mice (Tg2576) [9].

Another ND we are going to discuss is HD. HD is a hereditary condition that typically manifests in mid-life and is inherited in an autosomal dominant pattern. The main features of this genetic disorder include involuntary choreiform movements, progressive cognitive deterioration, and various psychiatric symptoms. The pathogenic mutation of this disease involves abnormal expansion of CAG trinucleotide repeats in exon 1 of the Huntington gene (HTT) on chromosome 4 (CAG > 40). The extended DNA can result in abnormal structure of protein. Then the protein can form insoluble aggregates which finally lead to neuron apoptosis and atrophy of the specific brain areas [10].

Huntington's disease currently has little effective treatments. Current medications mainly focus on alleviating symptoms such as Hyperkinesia (unwanted and excess movement), rigidity, cognitive impairment and so on. For treating the Hyperkinesia, now some approved drugs are Tetrabenazine (dopamine modulator), Olanzapine (dopamine antagonist), Amantadine (anti-glutamatergic drugs) [10]. As for the treatment of non-motor symptoms, Memantine (NMDA antagonist) was reported to have potential benefits in HD patients with cognitive impairment. Its ability of stabilizing overall level of glutamate neurotransmission helps in alleviating glutamate-induced excitotoxicity and reducing neurodegeneration and death of striatal neurons. Beside Amantadine, some antidepressant medicines such as selective serotonin reuptake inhibitors have been utilized to alleviate depression symptoms.

Because genetic mutation is the root cause of Huntington's disease, scientists are also attempting to use gene therapy to treat HD. Some researchers attempt to use RNA interference (RNAi) techniques to decrease the production of mutant huntingtin protein, which may potentially stop the progression of the disease [11]. This gene therapy aimed at altering the expression level of Huntington protein and this can be achieved through the editing of DNA or RNA.

At present, there are researches about the potential of using antisense oligonucleotides (ASOs) to decrease the expression level of HTT gene in order to relief or prevent the symptoms of HD. Antisense oligonucleotides (ASOs) are single-stranded oligonucleotide molecules, typically containing 15-25 nucleotides. Upon entering cells, they bind to complementary target mRNA through the principle of base pairing under the action of ribonuclease H1, thereby inhibiting the expression of the target gene. Some experiments have shown that ASOs can effectively decrease the HTT gene expression in animal model [12]. Additionally, the decrease in HTT protein can result in an improvement in pathology in

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HD's animal models. This success has brought hope for the clinical use of ASOs in treating HD. And now, there are some ASO-based products that are being researched in clinical stage.

Tominersen, developed in collaboration by Roche and Ionis Pharmaceuticals, is a non-allele specific ASO that targets both wild-type and mutant HTT mRNA. Phase I/IIa clinical trial results demonstrated that intrathecal administration of Tominersen effectively reduces mutant HTT protein levels in the cerebrospinal fluid (CSF) of Huntington's disease (HD) patients in a dose-dependent manner. Observations in subjects receiving doses of 90 mg and 120 mg showed approximately 40% reduction in CSF mHTT levels compared to baseline. However, subsequent Phase III trials revealed significant worsening of clinical symptoms such as motor function and cognition in participants receiving the 120 mg dose, along with elevated NfL levels, leading to early termination of the project [13].

Within the HTT gene, specific single nucleotide polymorphisms (SNPs) are frequently associated with CAG repeat expansion alleles. Consequently, Wave Life Sciences and Takeda jointly developed three ASOs potentially exhibiting allele-specificity. ASOs targeting rs362307 and rs362331 completed Phase 1b/2a clinical trials to assess resistance, pharmacokinetics, pharmacodynamics, and safety. However, these ASOs did not reduce mHTT levels in the CSF after intrathecal administration, resulting in trial termination. Another allele-specific ASO, WVE-003, targets an undisclosed SNP3. In animal studies, WVE-003 reduced mHTT in HD model mice by 50% and maintained efficacy for 3 months. Phase I trials began in 2021, with completion expected by December 2024. Mid-term reports indicate that after 85 days of administration, CSF mHTT levels decreased by approximately 22% from baseline in the 30 mg and 60 mg dose groups, while levels of wt HTT remained unchanged, demonstrating good allele-specificity.

ASOs like WVE-120101 and WVE-120102 rely on a single nucleotide mismatch to differentiate between mutant and wild-type alleles effectively. Theoretically, higher numbers of nucleotide mismatches enhance the efficiency of distinguishing between alleles. Therefore, insertional/deletional polymorphisms (indels) are also noteworthy targets, as they can introduce differences of 2 to 17 nucleotides between HTT alleles. ASO WVE-003, targeting undisclosed SNP3, likely falls into this category of polymorphisms. Moreover, current clinical trials primarily depend on intrathecal administration, limiting ASO application. Hence, finding more accessible routes for ASOs to reach the central nervous system is a critical focus of research.

Additionally, Vico Therapeutics' VO659 is another allele-specific ASO currently undergoing clinical trials for HD. Details regarding its specific structure and modifications have not been disclosed. Unlike other ASOs, VO659 targets CAG repeat sequences to identify and degrade mRNA, exhibiting high specificity for alleles with CAG expansions, potentially effective against CAG expansion diseases like SCA1, SCA3, and HD. The Phase I/II open-label, dose escalation trial is currently underway to evaluate safety and tolerability in early HD patients and mild to moderate SCA1, SCA3 patients. These preclinical and clinical experiments bring us insight into the ASO in HD treatment, which has promising future to overcome the shortcomings of traditional treatments.

4. Conclusion

The article mainly discusses about the current situation of NDs and introduction of several emerging gene treatments. A number of emerging therapeutic technologies for neurodegenerative diseases, such as epigenetic interventions through acetylation/deacetylation, gene therapies that target specific mRNAs or non-coding RNAs, and photo biomodulation therapies that can act on brain tissue. These potential gene treatments have some unique advantages and bring us hope for the cure of the NDs. Although these gene technology encounter some difficulties in developing practical clinical product, they are still promising and are potential to be further developed.

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