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Current Therapy and Challenges for Neurodegenerative Diseases

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Abstract. Neurodegenerative diseases are a group of diseases characterized by progressive loss and dysfunction of neurons, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, among others. Neurodegenerative diseases can be studied using epidemiology, which is the science of studying the distribution, effects and determinants of diseases, health conditions and events in a population, as well as countermeasures and measures for the prevention and control of diseases and the promotion of health. The incidence rate of a disease can be obtained by epidemiological studies, which is an indicator of the number of new cases in a population. This indicator is similar to the incidence rate and indicates the severity of the epidemic over a relatively short period of time. The incidence of neurodegenerative diseases increases with age, placing a huge burden on patients and their families. In recent years, with the deepening of research into the mechanisms of neurodegenerative diseases, scientists have gradually revealed the complex biological processes behind these diseases and developed a number of potential treatment strategies. This article will provide an overview of the current state of neurodegenerative disease research, recent advances, therapeutic method, and future challenges.

Keywords: Neurodegenerative diseases; therapy; challenges.

1. Introduction

Neurodegenerative diseases are a group of diseases caused by degeneration and dysfunction of the cells and tissues of the central nervous system, mainly including Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy. A common clinical manifestation of these diseases is cognitive decline. Neurodegenerative diseases are more common in the elderly. As population aging is aggravating, neurodegenerative diseases have aroused increasing concern since they seriously affect human health and quality of life [1]. Both AD and PD are widely affecting the elderly. Other diseases, such as Huntington's disease, different types of spinocerebellar ataxia, amyotrophic lateral sclerosis, and spinal muscular atrophy, have a relatively low incidence, but can also have a serious impact on the lives of patients.

In general, the incidence of neurodegenerative diseases is high and is on the rise as the population ages. Neurodegenerative diseases have become an important issue in global public health. Currently, treatments for neurodegenerative diseases focus on relieving symptoms and delaying disease progression. In drug development, resveratrol has received attention for its neuroprotective, anti-inflammatory and antioxidant properties. Studies have shown that resveratrol can reduce Aβ peptide aggregation and toxicity, stimulate neurogenesis and inhibit hippocampus degeneration [2]. In addition, stem cell therapy also shows great potential in the treatment of neurodegenerative diseases, especially ectodermal mesenchymal stem cells, which have unique advantages in spinal cord injury repair and neurodegenerative disease treatment due to their abundant sources, convenient acquisition and good nerve cell differentiation [3].

Although remarkable progress has been made in the study of neurodegenerative diseases, there is still a lack of effective cures. Future research is needed to further understand the pathological mechanisms of the disease, especially the interaction of genetic and environmental factors. In addition, developing new animal models and exploring stem cell-based regenerative medicine and precision medicine strategies will be key to overcoming current challenges. With the continuous development of science

and technology, we have reason to believe that greater breakthroughs will be made in the treatment of neurodegenerative diseases in the future.

2. Therapy for Neurodegenerative Diseases

2.1. CAR-T

Cell therapy refers to the treatment in which human autologous, allogenic or xenogenic (non-human) cells are applied after being manipulated in vitro and re-introduced (or implanted) into the human body. Among them, chimeric antigen receptor T-cell immunotherapy (CAR T-cell therapy) is a recently emerging adoptive cell immunotherapy that mainly combines the specificity of chimeric antigen receptor with the immune function of T cells, and then targets and kills malignant tumor cells through specific recognition [4].

The basic structure of CAR consists of extracellular region, transmembrane region and intracellular region. The extracellular region is mainly the light chain heavy chain variable region sequence (scFv) of monoclonal antibody. scFv can directly recognize TAA in a non-MHC-restricted way, and transduces signals through intracellular signal domain to activate effector T cells. Such as CD19scFv, CD33scFv and so on. The transmembrane region is mainly type I transmembrane proteins, such as CD4, CD8, CD28. The intracellular signaling region of CAR is the Immunoreceptor tyrosinebased activation motif (ITAM). It is usually the ζ chain of TCR/CD3 or the γ chain of FcεRI, and its role is to transmit activation and co-stimulatory signals to T cells. The transmembrane region of CAR is generally composed of homologous or heterologous dimer membrane proteins such as CD3, CD8 or CD28. The hinge region in the transmembrane region can connect the extracellular region with the intracellular region. At present, the CAR has developed from a generation of cars to four generations since Gross was proposed in 1989 [5].

The gene sequence of antibody variable region and intracellular signal region were identified by genetic engineering technology. The list is reassembled outside the human body and then transfected with a recombinant substance that will encode the CAR gene. The granules are transferred into the patient's T lymphocytes so that the T cell surface expresses the antigen. Expression specific chimerism of receptor protein after purification and large-scale amplification in vitroAntigen receptor T cells are called CAR T cells. CAR-T cell immunotherapy. Therapy is the use of genetic engineering methods that will identify the target antigen with a single chain antibody. Spacer regions, transmembrane motifs and T cell activation motifs are integrated and utilized. The fusion gene modified T cells not only can recognize and bind antigens specifically, but also have the ability of T cell self-renewal and killing [3, 5].

2.2. AAV

AVV is a non-pathogenic virus that has been genetically engineered to serve as a vector for gene therapy. The AAV virus consists of an icosahedral protein capsid with a diameter of about 26nm and a single-stranded DNA genome with a size of about 4.7kb. Inverted Terminal Repeats (ITR) with a T-shape at both ends, the ITR serves as the origin and packaging signal of viral replication, The two ITRs contain REP and CAP genes. The REP gene is responsible for encoding four proteins required for viral replication and regulation by molecular mass. Give them names: Rep78, Rep68, Rep52 and Rep40; The CAP gene is responsible for encoding the VP1, VP2 and VP3 proteins that make up the capsid, the viral coat. The shell was formed by polymerization of 60 capsid protein monomers in a ratio of 1:1:10 (VP1: VP2: VP3). In addition, the embedded part encodes an assembly activation AAP used to facilitate the assembly of viral particles. The AAV genome is mainly found in the nucleus Dissociated circular dsDNA forms exist, thus maintaining stable gene expression.

2.3. CRISPR/Cas

The CRISPR/Cas system consists of two core components: CRISPR sequence and Cas protein. The CRISPR sequence consists of a series of short highly conserved forward repeats with spacers of similar length. These repeat sequences typically consist of 28-37 base pairs, while interval sequences typically consist of 32-38 base pairs. The front end of the CRISPR sequence has an AT-rich leader sequence, which is considered to be the promoter region of CRISPR, responsible for initiating the transcription of downstream repeat sequences and interval sequences, and the transcription product is CRISPR RNA (crRNA). Cas proteins are a diverse family of proteins responsible for processing crRNA, forming complexes with crRNA, recognizing and binding target DNA, and thus cutting foreign genetic material. Among them, the Cas9 protein is the main effector protein in the CRISPR/Cas9 system, responsible for introducing double-strand breaks (DSBS) at target sites, which trigger the cell's DNA repair mechanism, leading to gene elimination, insertion, or other modifications.

The principle of CRISPR/Cas system can be divided into three phases: the adaptation phase, the expression phase and the interference phase. In the adaptive phase, when a bacterium or archaea is invaded by a phage or plasmid, its immune system captures a short DNA fragment of the invader (protospacer) and integrates it into the spacer sequence of the CRISPR sequence, forming a new spacer. This process is similar to flagging foreign invaders for subsequent identification and defense. During the expression phase, CRISPR sequences are transcribed into pre-crRNA and subsequently processed into mature crRNA. crRNA can form complexes with Cas proteins to prepare for subsequent targeted cleavage. In the interference phase, the complex formed by the mature crRNA and Cas protein is able to recognize and bind to foreign DNA that complements the crRNA sequence. Under the action of the Cas9 protein, the double strand of the target DNA is cut, forming a DSB. The cell's own DNA repair mechanisms attempt to repair this break, potentially introducing gene elimination, insertion, or other modifications to defend against foreign genetic material [6].

3. Preclinical Studies to Clinical Trails

3.1. Alzheimer’s Disease

Alzheimer’s disease is one of the most common neurodegenerative diseases that primarily affects the elderly. The global prevalence is 4-7%, and the prevalence in people over 65 years of age is about 4-7%. The occurrence of neurodegenerative diseases is usually related to many factors such as genetics, environmental factors and lifestyle. An important pathological feature of Alzheimer's disease (AD) is the abnormal aggregation of beta-amyloid protein (Aβ) and the formation of neuronal fiber tangles. In recent years, scientists have proposed a probabilistic model of AD, emphasizing the modification of the amyloid hypothesis, suggesting that the three variants of AD (autosomal dominant AD, APOE ε4-related sporadic AD, and APOE ε4-independent sporadic AD) have different pathophysiological cascade weights and environmental factors [7]. This model contributes to a better understanding of the complex biology of AD and the development of more effective treatment strategies.

The deposition of beta-amyloid protein outside of nerve cells to form large senile plaques (SP), and the accumulation of hyperphosphorylated tau protein inside nerve cells to form neurofibrillary tangles (NFT) have long been considered the most characteristic pathological changes of AD [8]. For CAR-T cells, different targets determine different recognition ranges [4]. The study shows that CAR-T cells can be engineered to specifically recognize A3 plaques, slowing or stopping the development of AD by removing these plaques. Leuchtenburg et al. reported a study in a mouse model where the successful use of anti-A3 CAR-T cells reduced A3 plaque accumulation and improved cognitive function in mice [9].

3.2. Parkinson’s Disease

Parkinson's Disease is a neurodegenerative disease characterized by movement disorders that primarily affect middle-aged and older adults. The overall global incidence is 0.1-0.2%, and the incidence begins to rise sharply after the age of 50, from 0.4% in the age of 50-54 to 4% in the age of 80 and older. Parkinson's disease (PD) is closely related to the misfolding and aggregation of alpha-synuclein. Studies have shown that alpha-synuclein transmission between neurons may be involved in disease progression [10]. In addition, mitochondrial dysfunction, oxidative stress and inflammatory response are also considered to be important mechanisms of PD pathogenesis.

Loss of dopaminergic neurons in nigra striatum is a typical pathological feature of most early PD patients [11]. Recently, there have been attempts to promote the regeneration or protection of dopaminergic neurons through CAR T cell therapy. Specific CAR T cells can recognize and attack those pathological proteins that cause neuronal death, such as A-synuclein, while secreting neurotrophic factors that support neuronal survival and regeneration [12].

In the field of PD therapy, AAV vectors are primarily used to deliver therapeutic genes, such as neurotrophic factors or genes that code for specific enzymes to compensate for the loss of dopaminergic neurons. For example, delivery of genes encoding aromatic amino acid decarboxylase (AADC) can increase dopamine synthesis, which improves PD symptoms. A number of preclinical studies have shown that AAV-mediated AADC gene therapy can significantly improve motor function in PD model animals, and this improvement effect is long-term.

In addition, AAV vectors can also be used to deliver mirnas or shrnas to silence specific genes that cause PD. For example, abnormal aggregation of α-synuclein (α-syn) is an important pathological feature of PD. Delivery of shRNA targeting alpha-SYN via AAV vector can effectively reduce its expression, thereby alleviating PD symptoms [13].

CRISPR/Cas technology is a revolutionary gene editing tool that enables precise modification of the genome, opening up new possibilities for treating genetic diseases [6]. In the PD field, CRISPR/Cas technology is mainly used to correct genetic mutations that cause PD. For example, mutations in the LRRK2 gene are associated with familial PD. Using CRISPR/Cas technology, LRRK2 gene mutations can be corrected directly within patient cells, thereby preventing or treating PD [14].

4. Conclusion

Although CAR-T cell therapy has shown great potential for application in neurodegenerative diseases, there are still many challenges. While recognizing and attacking pathological proteins, CAR-T can damage normal tissues with low expression of target antigens, resulting in off-target effects, which can endanger patients' lives in severe cases. First, the complexity of the nervous system requires highly specific CAR designs to avoid damage to normal nervous tissue. Secondly, the persistence and functional maintenance of CAR-T cells in the central nervous system are also issues that need to be addressed. In addition, ethical and safety issues cannot be ignored.

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