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The Application and Potential of CRISPR-Cas9 in the Treatment of Parkinson's Disease

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Abstract. Parkinson's disease (PD) is a progressive neurodegenerative disorder that contains the significant characters of gradual degeneration of dopaminergic neurons in the substantia nigra of the human brain. This disease significantly affects patients' lives significantly affecting the degeneration of movement and consciousness. Despite a large amount of research results, there is still no way that can fully cure PD. The genetic factor has played a crucial role in the pathogenesis of PD, with mutations in genes such as SNCA, Parkin, PINK1, DJ-1 and LRRK2 being closely related to the disease. It highlights the potential of gene targeting therapy. CRISPR-Cas 9 is a revolutionary gene editing tool, first found in bacteria. Its flexibility and feasibility give hope to the treatment of PD. The review will discuss how CRISPR-Cas9 can be used in the PD treatment and its application with these gene editing targets. In addition, CRISPR-Cas 9, this kind of gene therapy, is also facing some big challenges like off-target activity, human body inflammation, and ethical problems. In conclusion, to make CRISPR-Cas 9 and PD combined treatment can have a good development for the clinic, it still needs to overcome a lot of technological barriers and moral controversy.

Keywords: Parkinson dieases, CRISPR-Cas9, gene therapy, application

1. Introduction

A progressive neurodegenerative disorder, Parkinson's disease (PD) affects the brain and human motor function. It typically occurs with aging. There are over 10 million people across the world who have been disturbed by Parkinson's disease. The exact causes of PD is still unclear but the probable causes are the death of the brain cell that contirled the production of dopamine under the part in human brain that called nigra. Dopamine is a crucial neurotransmitter that is involved in regulating movement. PD also has multiple and complex etiologies, including genetic problems, mitochondrial dysfunction, oxidative stress, and neuroinflammation. To date, no treatment has been found that can stop or reverse the progression of PD. In recent years, scientists have been using a new genetic editing tool called CRISPR-Cas9 to study and find the treatment of diseases like PD. CRISPR was first detected in bacteria as a portion of the defense system. It works by using guiding RNA to lead the Cas 9 protein that can cut the DNA at its specific spot. This genetic editing tool, compared with the early gene editing tools such as transcription activator-like effector nucleases (TALENs) and, finger nucleases (ZFNs), CRISPR-Cas 9 offers greater simplicity, lower cost, higher

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efficiency, and it is easily designed; these make it an attractive platform for disease modeling and genetic therapy improvement.

During PD research, CRISPR-Cas9 technology has been applied to the animal models, which helps scientists to have a better understanding of the genetic and molecular mechanisms of the treatment of assorted diseases. These include knocking out Parkin, PINK1, and DJ-1, and other vital parts of the pathogenic gene in other diseases. CRISPR-Cas 9 is applicable for curing PD by knocking out the mutation and the targeted gene. Other than that, CRISPR-Cas9 can provide a special way for treatment, like to build new and healthy brain cells as a treatment for PD by combining CRISPR and induced pluripotent stem cells (iPSCs). Nevertheless, CRISPR-based therapeutics are also facing some significant challenges, including the risk of off-target mutation, moral contribute with editing the human germline gene, and the biggest disadvantage of gene editing is that it can only prevent the appearance of a disease but can not cure existing patients. Except for using gene editing directly, the researchers are still exploring ways to develop the accuracy and security of CRISPR-Cas 9, which includes the Cas9 variants and a more optimal design of guided RNA to minimise the off-target activity. Increasing the permeability of the BBB can help with the Cas9 entering the nervous system successfully. The Prime editing and base editing help scientists to edit DNA without breaking the DNA strand. The review will argue the application and potential of CRISPR-Cas9 in the treatment of Parkinson's disease and look forward to the future of combining CRISPR with other therapies to treat more diseases.

2. PD-related gene editing

Parkinson's disease (PD) is a complicated neurodegenerative disorder that have the main character of rigidity, bradykinesia and postureal instability that shown the gradual death with the dopaminergic neurons in the substantia nigra. The treatment for curing PD has not been discovered yet. However, based on the extensive research results, the mutations that cause PD are most likely to originate from SNCA, Parkin, PINK1, DJ-1and LRRK2 [1].

The SNCA gene encodes the α-synuclein protein in the human brain. which is the main contributor of the PD pathology, due to its tendency to form the toxic protein aggregates and make the mutation protein. This will form the Lewy bodies. To treat PD, decreasing the concentration of SNCA is a really important way [1]. Parkin and PINK1 genes play a role in clearing damaged mitochondria, but with the mutation of these two proteins, the damaged mitochondria can not be eliminated. It will lead to the large amount of accumulation of mitochondria which will increase the oxidative stress in cells, causes the dopamine nureone dieing, affact the substantia nigra in the brain. The PD can appear. Building the model of double knock out of PINK1 and Parkin is the critical method to study the cellular consequences of impaired mitochondrial quality control. This model can be combined with CRISPR-Cas9 to be used as a treatment for PD. Double knockout gives CRISPR-Cas 9 a good platform and is ideal to knock out the PINK1 and Parkin genes [2]. DJ-1 plays a role as a protective protein of the neuron; its absence will render the cell unable to clear ROS, which will increase oxidative stress [3]. DJ-1 helped to maintain the mitochondrial membrane potential and the energy metabolism. After the absence of the DJ-1, the efficiency of the mitochondria is reduced, leading to insufficient energy provision. Affect the dopamine neuron. Other than these mutational sites, and potential pathogenesis to PD. Leucine-rich repeat kinase(LRRK2) is one of the critical pathogeneses of PD. The mutation like G20195 will enhance the enzyme activity of LRRK2 and lead to the autophagy-lysosomal pathway and resulting in a high concentration of α-synuclein. Other than that, the abnormal LRRK2 can influence mitochondrial homeostasis,

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promoting oxidative stress and making dopaminergic neurons more susceptible to degeneration. LRRK2 remains a promising genetic therapy target for PD and other related diseases [4].

The new way that combines CRISPR-Cas9 with iPSCs can cure the existing patient with PD. This technique allows the mutated cell and gene to be transplanted, and cure the mutated gene at the site of the patient's external body, and then transplanted back to the patient [5]. This combination has the most practical way for curing the existing PD, and causes the less damage to patients.

3. The principle of CRISPR-Cas9 and technical evolution

CRISPR-Cas9 is a convenient tool for genetic editing. It was first discovered in the bacteria named Streptococcus pyogenes. This bacterium can identify and cut the specific exogenous DNA. The scientist made the modification based on this identity that can help the world solve many more medical problems like PD [1]. The essence of CRISPR-Cas9 is using the single-stranded RNA(sgRNA) that can direct the Cas9 protein to a definite genomic locus. Once the Cas9 protein has bonded with this locus, it can introduce a double-stranded break(DSB) at that target site. A cell can obtain its genetic knockout or mutation repair by non-homologous end joining (NHEJ) or homology-directed repair (HDR) [3]. In comparison with the previous TALENs and ZFNs genetic editors, CRISPR-Cas 9 gets the benefit of its easy design, lower costs, and higher efficiency [2]. Since it has been discovered, CRISPR-Cas 9 has become the most widely used gene editing tool; its flexibility and designability allow scientists to use it in bacteria or human cells, and other various cells.

With the development of the research, CRISPR has shown its constant involvement in security and flexibility. One of the major innovations is base editors, which can make a single base pair change, with no need for the break of the DNA double strand. Base editing improved the security and accuracy of gene editing silently. It decreases the probability of accidents of mutation and chromosomal rearrangement [6,7]. Prime editing is a better way for genome editing than base editing. It can substitute, insert, or delete any base pair. It has higher precision. However, it will change the DNA double strand and may damage it. Prime editing has a more practical function, but it is not as safe as base editing [7]. To make CRISPR more applicable to central nervous system disease. The researchers have also discovered the multiple delivery strategy. These included adeno-associated viruses (AAVs), lipid nanoparticles, and exosome-mediated delivery. These made a large success in targeting the neuronal population [8].

Expect the DNA edition, the CRISPR toolbox has expanded to RNA targeting systems like Cas13, it enable to the control of RNA expression temporarily without changing the genome. These characteristics render safe long-term genomic editing in post-mitotic cells such as neurons. Based on the reversibility of Cas13, it gave a benefit for the gene that does not need to be changed permanently by just repressing the expression for a short period to anesthetize symptoms [5]. CRISPR-Cas 9 has a vast prospect and potential, but the upcoming challenges, like off-target activity, immunogenicity to the human body, and ethical problems, are still waiting to be solved. Therefore, to make the preclinical translation, there are still a lot of problems that need to be addressed [1,3].

4. The challenges and ethical reflection of CRISPR-Cas 9

Although CRISPR-Cas 9 has shown its great potential in PD treatment, it is still facing a lot of challenges, including technical development and ethical challenges. The main problems include off-target activity, delivery inefficiencies, immunogenic responses, and serious ethical concerns,

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especially when contemplating clinical use. The off-target activity is the main problem that CRISPR faces, even though the highly optimized gRNA and high-fidelity Cas9 can be damaged by the DNA at the non-targeting locus. The damage can increase the cancerous risk and disrupt key genetic functions [1]. The damage is not reversible, especially the damage to the central nervous system when it acts as a treatment for PD. Other than that, the current method to measure the off-target activity is still waiting to be perfected to avoid and minimise the unexpected editing in the genome is of great significance.

Other than that, the delivery system is inefficient. The blood-brain barrier (BBB) has been restricted to the central nervous system. The CRISPR-Cas9 components, like the Cas9 protein, a large molecules. Based on the characteristics of the BBB, the large protein is not allowed to be passed and transported into the central nervous system [9]. For now, CRISPR-Cas 9 is still not suitable for use in the treatment related to the central nervous system. In order to overcome this limitation, researchers are still discovering alternatives such as engineering viral vectors, lipid nanoparticles, and other methods. These means can help to better cross the BBB and reach the neuron safely for treating diseases. The immunogenetic problem should also be noted. The Cas9 protein has been discovered in bacterial proteins, which are easily detected and attacked by the human immune system, and lead to unexpected treatment results and partial inflammation [6]. This inflammation problem can not only lower the treatment efficacy, but also possibly bring more serious diseases to the sensitive patients.

The ethical problem with CRISPR-Cas9 also can not be ignored. Although the current PD treatment with genetic editing has focused on the somatic cell, the controversy of human genetic editing has existed constantly. When it involves the germ cell. It still remains controversial due to its effect on the future generation, and may potentially be misused for the enhancement of human ability [10]. These concerns have led to a deeper conversation about fairness, informed consent, and long-term social impact. The deeper concern is to find the line between treatment and enhancement; this is the largest controversy of gene editing. People can use this way to enhance their human body ability, make a new human with higher flexibility, better memory, or a healthier body with no illness for their whole life.

5. Conclusion

In conclusion, Parkinson's disease is a convoluted and incurable neurodegenerative disorder that still poses a serious threat to the quality of life for patients worldwide. Existing surgical treatments and medications offer only limited symptom relief and do not provide a cure method for Parkinson's disease. Researchers are still working to find better and more innovative ways to treat this disease, including CRISPR-Cas9, a new and practical genetic editing tool. Studies suggest that the pathogenesis of Parkinson's disease is closely related to certain mutated genes that can potentially be edited using CRISPR-Cas9, which presents developmental opportunities for this technology. However, to successfully implement CRISPR-Cas9 in clinical settings, many challenges remain. Off-target effects, low delivery efficiency, and immune responses all raise concerns about safety and effectiveness. Additionally, gene editing involving human reproduction raises ethical issues. The idea of human body enhancement has also sparked extensive debates about fairness and long-term impacts. Future research should focus on improving the Cas9 protein, optimizing delivery methods across the BBB, and developing variants, such as base editing and prime editing. It is likewise crucial to formulate the regulatory norms and promote full conversation between scientists and the public to ensure the answerablely use of this revolutionary technology.

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