Developing Treatments for Parkinson's and Alzheimer's Disease Using CRISPR

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Scientists are working to tackle the growing epidemic of neurological disorders. The recent discovery of the Clustered Regularly Interspaced Short Palindromic Repeats or CRISPR system has created opportunities for researchers to regulate gene expression by altering genes on a molecular level. Current treatments only treat the symptoms presented by patients and not the root cause of the disease. The CRISPR-Cas9 system has become more popular for its advantageous features such as its high efficiency, low cost, and simplicity. With CRISPR, genes and their mutations linked to Alzheimer's Disease and Parkinson's Disease can be altered or deleted to regulate gene expression and slow or stop the progression of the diseases. In this literature review, the details of CRISPR, Alzheimer's Disease, and Parkinson's Disease will be explained. This review will look at how CRISPR is being applied in experiments to develop treatments for patients, what the effects of the treatments are, and the limitations that need to be considered when moving forward with this technology.

Introduction

Progression in the field of medicine has led to an increase in the life expectancy of humans. However, as the lifespan of the average person has increased, so has the prevalence of neurological degenerative diseases in the human population for individuals over the age of 60. Neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are characterized by the deterioration of the brain due to damaged or dead neurons[1]. The decline in the brain's cognitive function affects the functionality of the nervous system. In turn, people with AD experience symptoms of dementia and impaired sensory processing while people with PD experience problems with muscle control, including tremors and rigidity[2,3]. As the number of people living with AD above the age of 65 doubles every 5 years and the number of those with PD has doubled in the last 25 years, there is a need to address the increasing presence of AD and PD in society[4,5].

The CRISPR-Cas9 system was observed in multiple bacterial species as an adaptive defense system against invading phages[6]. In the CRISPR system, the Cas9 enzyme induces double-stranded breaks (DSBs) in DNA. These DSBs are then repaired through either nonhomologous end-joining (NHEJ) or homology-directed repair (HDR) when a DNA ligase and DNA repair template is provided. These repair processes can lead to specific insertions or deletions (indels) in the targeted genes, which can either disrupt gene function or introduce desired modifications to regulate gene expression[7]. However, NHEJ is error-prone and while HDR is more effective, it usually occurs during cell replication. This can be problematic because Alzheimer's and Parkinson's disease tend to develop at a later stage in life, during which many neurons are post-mitotic[1]. The gene-editing system shows promise in treating some of the causes that lead to neurodegenerative diseases by halting or even reversing the degeneration of neurons. This literature review will explore the capabilities of the CRISPR-Cas9 system and how they can potentially slow or stop the progression of neurodegeneration in AD and PD, alleviate the debilitating symptoms that come with these diseases, and reduce disease incidence.

Overview of CRISPR-Cas9 and Neurodegenerative Diseases

Factors Linked to Alzheimer's & Parkinson's Disease

The development of neurological diseases like AD and PD is affected by several factors that include genetics, oxidative stress, environmental interactions, and most prominently, aging of population. During the development of AD, amyloid beta ($A\beta$) and tau proteins build up in the brain to form amyloid plaques and tau tangles. These pathological structures damage brain regions necessary for memory formation, leading to the onset of dementia symptoms[2]. Patients with AD are categorized into two subtypes: early-onset AD (EOAD) patients under the age of 65, and late-onset (LOAD) or sporadic AD (SAD) patients 65 and above. The majority of EOAD cases are associated with altered levels of the $A\beta 42/40$ ratio due to inherited mutations in the amyloid-β precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2) genes[7,8]. In contrast, the complexity of the factors behind sporadic or LOAD have made it difficult

to identify its pathogenicity. This phenotype is most likely polygenic, meaning more than one gene contributes to its incidence and progression. Genes such as apolipoprotein E4 (APOE), clusterin, complement component (3b/4b) receptor 1 (CR1), sortilin-related receptor-1, ATP-binding cassette subfamily A member 7 (ABCA7), CD33, and triggering receptor expressed on myeloid cells 2 (TREM2) are linked to its progression[7].

This review looks at whether CRISPR-Cas9 can edit single genes connected to EOAD to correct altered levels of the Aβ42/40 ratio and thereby decrease the accumulation of Aβ and tau proteins. Establishing the efficacy of CRISPR Cas9 EOAD can support the creation of low cost and effective models of mutations to understand the pathology of complex polygenic LOAD. Understanding the pathology of LOAD can have a much broader impact due to higher prevalence in society. Finding that CRISPR works on EOAD genes can in turn help to set up future studies editing multiple genes with CRISPR for LOAD cases. When developing treatments targeting mutated genes, working towards prioritizing clinical trials for LOAD can create a broader impact, since genes associated with sporadic Alzheimer's disease are more prevalent than others.

Additionally, data from clinical and experimental studies have found neuroinflammation, oxidative stress, dysregulated protein degradation, and mitochondrial dysfunction to primarily cause PD neurodegeneration[1]. Cognitive and motor impairment in Parkinson's disease results from the degradation of dopaminergic neurons (DNs) in the nigrostriatal pathway. The loss of DNs can result in the formation of Lewy bodies (LBs) primarily made of misfolded α-synuclein proteins[1]. Because the LBs accumulate in areas of the brain involved in cognition, memory, and movement, neuronal death occurs, impacting motor and non-motor functions, such as sleep, in PD patients[9]. PD can be classified as sporadic or familial. The familial type is linked to the mutations of heritable genes, and the sporadic type is related to gene variants that increase one's susceptibility to PD[10]. Familial PD is associated with mutations in inherited genes such as SNCA, Parkin, PINK1, DJ-1, and LRRK2, and it accounts for up to 10-15% of all cases.

Although the exact biological mechanism of the sporadic type of PD remains unclear, several environmental and genetic risk factors have been associated with it. Notably, variations in the SNCA, Parkin, and LRRK2 genes also implicated in the familial type of PD have been observed to increase the risk of developing the sporadic form of the disease[11,12]. Discovering how AD and PD develop in the brain has helped researchers develop treatments targeting genes associated with the diseases. However, certainty on the exact genes that cause the diseases can lead to the development of long-term solutions to augment existing treatments.

Current or Existing Treatments

Over the years, drug treatments and therapies have been developed to target the factors of neurodegeneration in AD and PD. Common treatments for AD include inhibitors of acetylcholinesterase (AChE) activity such as donepezil, rivastigmine, NMDA receptor antagonists like memantine, and galantamine. A high dose of monoclonal antibodies targeting β-amyloid (Aβ) plaques has been introduced as a therapy as well[13]. Although these treatments work towards controlling symptoms, they do not prevent, halt, or repair the neurodegeneration (see Table 1). Despite the efforts made in drug development to treat AD, clinical trials from 2002 through 2012 show a failure rate around 99%, which is higher compared to clinical trials testing drugs for other diseases during the period[8]. There are concerns over current therapeutic treatments regarding their effectiveness, safety, or stability for Alzheimer's disease patients. Limited knowledge of the pathophysiology of AD also prevents researchers from developing specific treatments that target some of the causative factors[8]. In PD, symptomatic medication therapy is a more common treatment since there are a limited number of effective disease-modifying treatments[1]. However, symptomatic treatments do not seem to be a viable, long-term solution as they do not fully address the underlying cause of the disease and are associated with multiple side effects. Researchers involved in cell replacement therapy demonstrated the feasibility of producing DNs from human embryonic stem cells (hESCs) and implanting them in animal PD models[1]. While the results revealed an increase in dopamine (DA) levels in the experimental animals, the technique has several issues that include concerns with the effectiveness and safety of the treatment in patients[1]. A commonality in these neurological diseases is that they are polygenic, meaning there are mutations of multiple genes. Mutations in disease-linked genes can cause toxic gain-of-function, which amplifies protein activity, or loss-of-function, which reduces protein activity—both of which can contribute to disease complications. With the gene-editing system CRISPR-Cas9, researchers could not only manage patient symptoms but mitigate neurodegeneration or restore neuronal function. While considering this possibility, it is important to note the challenges of off-target effects and treatment delivery still need to be addressed.

Overview of CRISPR and its Function

In the field of genome editing, zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have been the tools for gene editing before CRISPR emerged. When the RNA-guided CRISPR system was developed, more scientists were drawn to use the system due to its ease of use, high efficacy, low cost, and good repeatability. These benefits led the CRISPR-Cas gene-editing technique to become widely adopted. CRISPR-Cas is an adaptive immune system located in most bac-

Table 1 Current Treatments for Alzheimer's Disease

Type	Treatments	Application	Strengths	Limitations
Drug Treatments	AChE activity inhibitors (Donepezil, Rivastigmine) NMDA receptor antagonists (Memantine & Galantamine)	Targets neurodegenerative factors	Controls symptoms	1. Drug treatments do not prevent or repair neurodegeneration 2. No differentiation in treatment options for EOAD, LOAD, & SAD 3. High drug treatment failure rate
Disease-modifying Therapies	High dose monoclonal antibodies introduced as a therapy	Targets β amyloid plaque	Controls symptoms	1. Treatments not very effective 2. Limited knowledge of pathophysiology of AD 3. Often initiated too late to be impactful 4. Therapies don't prevent or repair neurodegeneration
Gene Editing (before CRISPR)	ZFNs, TALENs	ZFNs target the APOE4 allele and convert it from E4 to E3	Conversion of E4 to E3 reduces AD risk	—

Data in this table are adapted from N. C. Barman et al. (2020), R. Cooray et al. (2020), and S. Bhardwaj et al. (2021). AChE = acetylcholinesterase; NMDA = N-methyl-D-aspartate.

teria and archaea. The most commonly used CRISPR system comprises a single-guide RNA (sgRNA) and RNA-guided Cas9 endonuclease. The sgRNA is made of CRISPR crRNA and tracrRNA. When the Cas9 and sgRNA combine, they create a ribonucleoprotein (RNP) that can bind and cleave targeted DNA. In order to defend against viruses and phages, Cas9 proteins cut the foreign DNA into short fragments and the fragments are then integrated as new spacers into the CRISPR array. Once the CRISPR system detects the same foreign elements in the host, the crRNA pairs with the foreign DNA, and the Cas9 protein cleaves it. As the Cas9 protein binds to the target, a protospacer adjacent motif sequence is required to induce a double-stranded break. The break is either repaired through nonhomologous end-joining (NHEJ) or homology-directed repair (HDR). NHEJ can introduce random insertions or deletions without the need for a donor template to start the repairs, and is more efficient due to being active in nearly 90% of the cell cycle. However, HDR is precise and can alter the genome at target site through a donor DNA repair template[14]. Therefore, this powerful system has garnered the interest of researchers to develop treatments for genetic diseases and disorders.

Applications of CRISPR-Cas9

Application of CRISPR-Cas9 in Gene-Editing of Neurological Diseases

The CRISPR-Cas9 system has been widely adopted by the scientific community due to its efficiency in editing genes and correcting mutations. One application of the system (see Table 2) is to target the expression of genes linked to AD and PD. PSEN1 (presenilin 1) and PSEN2 (presenilin 2) are genes that encode components of the -secretase complex, cleaving APP. Inherited mutation in the PSEN1 and PSEN2 genes can result in elevated Aβ42 levels and an elevated Aβ42/40 ratio due to impaired amyloid metabolism. The higher ratio of Aβ42 can be more prone to aggregation, increasing the accumulation of amyloid plaques linked to EOAD[7,15]. With CRISPR-Cas9, one study targeted the PSEN1 gene to correct the Met146Val mutation linked to AD in a human neuroblastoma SH-SY5Y cell line. The PSEN1 gene is one of many that cause an imbalance in the Aβ42/40 ratio, linked to early-onset AD, and targeting the Met146Val mutation balanced Aβ42/40 levels. One study focused on the N141I mutation in the PSEN2 gene. Correcting this

Table 2 Results of Editing AD-linked Genes Using CRISPR-Cas9

Model	Gene	Mutation	Results
Human neuroblastoma SH-SY5Y cell line	PSEN1	Met146Val mutation	Balanced Aβ42/40 levels
Basal forebrain cholinergic neurons	PSEN2	N141I mutation	Normalized the levels of Aβ42/40
Hippocampus of transgenic mice	APP Swedish	Swedish mutation	Decrease in Aβ formation

Data in this table are adapted from V. V. Giau et al. (2018), N. C. Barman et al. (2020), and S. Bhardwaj et al. (2021).

mutation normalized the levels of Aβ42/40 in basal forebrain cholinergic neurons[7]. In the frequently targeted Swedish mutation, increased β-secretase 1 cleavage activity leads to increased production of Aβ and formation of plaques[8,15]. In one study, when a vector encoding APP-Swe-specific guide RNA and Cas9 was delivered into the hippocampus of transgenic mice using an adeno-associated viral (AAV) carrier, there was evidence of disruption in the APP Swedish gene, demonstrated by a decrease in Aβ formation[8]. The studies above highlight the potential of CRISPR-Cas9 to correct EOAD-associated mutations and mitigate Aβ in preclinical models. However, since AD is more predominant in those over 60 years old, studies on SAD have a greater potential to treat more individuals.

In an earlier study, zinc-finger nucleases were utilized to target the APOE4 allele and convert it from E4 to E3. While the E4 form of APOE increases the risk of AD, the E3 form has no apparent effect on the risk of AD (see Table 1). Bhardwaj et al. saw the potential for gene-editing technology such as CRISPR to target this allele in the future[15]. Wang et al. (2018) later demonstrated with the CRISPR-Cas9 system that altering APOE4, a contributor to AD, to APOE3, a harmless gene to the disease, prevents the onset of AD characteristics in the model system[8,16]. As another way to demonstrate the efficacy of CRISPR, Sun et al. edited endogenous APP at the extreme C-terminus. Inhibiting interactions with BACE1 within endosomes mitigated β cleavage and therefore Aβ generation[15]. Reducing Aβ generation prevents more amyloid plaques from building up in the brain and reduces the progression of AD. With developing treatments targeting the mutations behind the disease, a long-term solution to the disease seems possible.

Along with AD, the CRISPR-Cas9 system has been applied to mutations linked to the familial type or sporadic type of PD. Targeting the familial type genes, one study used Cas9 to alter the loss-of-function mutations from the Parkin, DJ-1, and PINK1 genes. The study was modeled in Bama miniature pigs because they share multiple characteristics of human anatomy and physiology. After treatment, the gene-edited piglets remained healthy and displayed normal behaviors at 10 months of age. The positive results from the treatment of the pigs signal progress toward testing this treatment in clinical trials[7,17]. Another gene that was targeted by researchers was the SNCA gene in PD patients to stop neurodegeneration in the substantia nigra (SN) region of the brain[18]. Since SNCA transcription is regulated by DNA methylation at intron 1, a CRISPR-dCas9 system was designed to specifically target and modify this region. By delivering the CRISPR system using a lentiviral vector in the model, researchers successfully achieved a downregulation of SNCA levels[1]. The CRISPR-Cas9 system can be used to delete mutations to prevent them from being expressed. As demonstrated by Hyung Ho Yoon et al. the A53T mutation in the SNCA gene was targeted in rats and using AAVs composed of a single guide RNA and SaCas9-KKH, the overexpression of α-synuclein was significantly reduced. This led to the reduction of symptoms typically associated with the overexpression of α-synuclein such as motor symptoms, dopaminergic neurodegeneration, and reactive microgliosis were also minimized[1,11,19]. Neurotoxin MPTP is a substance used to induce PD and its symptoms in vivo models, and the loss of dopaminergic neurons (DAergic) has been associated with PD because they control much of the body's voluntary movement[20,21]. The 13-kDa protein p13 induces mitochondrial dysfunction and related apoptosis. Inoue et al. reduced the expression of p13 using CRISPR-Cas9, and the mice with this protein deficiency displayed no motor dysfunction or DAergic neuron destruction following treatment with model neurotoxin MPTP[1]. Mammals such as rodents can be suited to studying PD pathogenesis and pathophysiology due to their complex nervous system, but shortcomings of different animal models can challenge the translation of results to humans. Animal models can fail to capture the entire course of the PD due to the short lifetimes of models. Understanding the effect of treatment during the whole course of the disease is essential to translating the treatment to humans as a long-term solution. Age plays an important part in PD pathology development, but the use of aged animal models in studies has likely been limited due to cost and time. Because the factor of age is not investigated in the models, this provides further limitation on clinical applicabil-

ity[22]. By selectively editing genes and mutations linked to PD, gene expression is altered, and defects in molecular pathways are corrected. These gene corrections functionally repair the disrupted biological pathways that contribute to PD progression, potentially leading to improvements in the condition of patients[1].

Using CRISPR to Create Models of Alzheimer's and Parkinson's for Testing Treatments

To test the efficacy of treatments developed, CRISPR can be used to generate models of neurodegenerative diseases such as AD and PD[7]. To generate a PD cellular model, Vermilyea et al. used CRISPR-Cas9 to introduce the mutation G2019S in the LRRK2 gene in induced pluripotent stem cells (iPSCs) from marmosets. iPSCs are derived from adult somatic cells and have been reprogrammed to be pluripotent or have the ability to develop into any type of cell[23]. The dopaminergic neurons had an increase in ROS production, decreased neuronal viability, and neurite complexity, successfully displaying the features of PD. A neuron model of PD can provide a more effective test of treatments and better display how the brains of PD patients are impacted by treatment. In vivo models with features of PD were developed using CRISPR-Cas9 to create Vps35 D620N knock-in mice[11]. Additionally, human iPSC neurons from PD patients with A53T and SNCA triplation were used by Chen et al. to observe the molecular role of SNCA in the nucleus[1]. The first modeling of AD mutations occurred in 2016 of the APP Swedish and PSEN1 M146V mutations. Using iPSCs, neural precursor cells, and neurons to observe human knock-in cell lines helped them analyze the Aβ42 levels and Aβ42/40 ratio. In another study using CRISPR-Cas9 to model, Paquet et al (2016) modeled APP and PSEN1 mutations of AD and demonstrated a more precise genome editing method using gRNA synthesis[7,24]. One limitation of iPSC-based neurons is during reprogramming, there is a loss of age and environment-dependent cellular signatures. When studying an age-related disease such as AD, the lack of an aged cellular environment limits the applicability of the results[25]. Developing treatments and conducting studies can be expensive and require special equipment. CRISPR can create specific models of the mutations behind AD and PD in a time and cost-effective way. The cost efficiency and ease of CRISPR model creation compared to older models can allow for more accurate and efficient testing and clinical trials.

Discussion

Potential and Challenges of CRISPR Methods

The discovery of CRISPR and its gene editing ability has expanded our capacity to edit genes with greater efficacy, feasibility, and efficiency. Along with its use in genetic alterations to affect gene expression, it can also be used to create in vivo and in vitro models for human disease modeling[1,11]. Despite the benefits of CRISPR, there are challenges that restrict scientists' ability to apply this technology in certain ways. Starting with our understanding of PD and AD, there has been much progress in identifying the genes and mutations associated with these diseases, but there is still much progress that needs to be made to identify the pathogenic mechanisms of the subtypes[1]. With the help of new model systems based on CRISPR-Cas9 and more experimentation, researchers can better understand the pathology of the subtypes of AD and PD along with figuring out the factors associated with them.

To target a larger range of cell lines, plasmids combining guide RNAs and Streptococcus pyogenes Cas9 (SpCas9) can be used. In doing so, the precision of treatments is enhanced and CRISPR can target a wider range of diseases to treat. However, the host body may react problematically to the plasmids with an immune response or the plasmids themselves may cause stress or toxic effects on the host cells[7]. One major concern is the frequency of off-target mutations. When editing DNA sequences, off-target effects can occur due to the system recognizing similar homologous sequences[7]. To reduce these effects, an appropriately low concentration of Cas9, more powerful guide RNAs, and Cas9 variants such as SpCas9 could contribute to the improvement of precise genome editing[1,7]. SpCas9-HF1, a variant of SpCas9, is especially effective at reducing off-target mutations compared to the wild-type[26].

Even though various viral and non-viral vectors have been developed for delivery, a standardized delivery system for CRISPR is still in progress. In AAV-mediated delivery, the CRISPR system's large size remains a challenge due to AAV's small packaging capacity of 4.7 kb[8]. SpCas9 is too large to package in a single AAV vector, but SaCas9 is small enough to fit, making it ideal for in vivo genome editing in the brain[27]. Rafii et al. (2014) showed that using an AAV serotype 2 to deliver NGF showed promising results as there was no evidence of accelerated decline after delivery. With no noticeable complications, this delivery method demonstrates potential. However, further studies are required to validate its long-term safety and efficacy in human subjects. Alternative delivery methods to AAV include lipid, polymeric, and Gold nanoparticles. These non-viral vectors have a better cost, efficacy, and are flexible in terms of the size of the transgenic part[8]. Another issue preventing CRISPR from being widespread in medicine are the potential immunological reactions that are activated within patients who receive CRISPR. In some cases, in vivo delivery using a viral vector can trigger an immune response from the host due to the integration of carriers into the host genome[8,28]. A study collected a sample of 34 human blood cells. There were antibodies found for SaCas9 in 79% of the samples and for SpCas9 in 65% of samples[1]. The presence of such antibodies suggests the immune

system has already been exposed to S. aureus and S. pyogenes during an infection. One way to potentially mitigate immune responses is by using transient Cas9 expression through nonviral delivery of mRNA which would shorten the time required for immune suppression [29].

There still remains the question of the possible long-term effects of gene editing, including whether these alterations are heritable and what the possible implications could be. With the homogenization of genes, there could be a loss of diversity in human genes as they are passed down to offspring [7]. Additionally, any mutagenesis unintentionally induced, such as off-target effects may be hard to spot and predict early on [1]. These long-term effects need to be observed over a period of time and addressed before this technology can be applied to the general public.

Methods

Research papers were mainly collected by searching the National Library of Medicine PubMed. Keywords such as "Alzheimer's Disease", "Parkinson's Disease", "CRISPR", and "CRISPR-Cas9" were used to find studies altering genes linked to the diseases. Terms such as "AAV" and "Induced Pluripotent Stem Cells" were combined with the previously mentioned keywords to discuss delivery methods and models for testing. "LOAD and EOAD Alzheimer's" as well as "Familial and Sporadic Parkinson's" were keywords used to find the prevalence of each type, risk factors, and genes linked to the disease. Symptoms of AD, PD, and lewy body dementia in PD patients were sourced from the National Institute on Aging and National Institute of Neurological Disorders and Stroke. Statistics on the prevalence of AD and PD in society were sourced from the CDC and WHO. Information on research designs and key findings were extracted from studies altering genes using CRISPR. Research papers for this literature review were selected based on the criterion of being published after the year 2000. The information was organized to show whether editing genes linked to AD and PD would slow or halt the progression of the disease. Data regarding the specific limitations of CRISPR were used in the discussion. In the research process, academic databases such as PubMed, ScienceDirect, peer-reviewed journals, official US government agency websites with a (.gov) domain, and international public health websites such as WHO have been reviewed.

Conclusion

CRISPR has enabled multiple applications in gene editing, including the ability to edit mutations and genes linked to diseases such as Alzheimer's and Parkinson's disease, both of which are increasingly concerning with their growing prevalence in the aging population. With the growing epidemic of neurological diseases, researchers are using CRISPR to slow or stop their progression. The CRISPR-Cas9 system is the most popular for its efficacy and ease of use in experiments. Focusing on the subtypes of AD and PD, researchers have targeted the mutations associated with each type by altering or deleting them. The results show that the expression of mutated genes leads to improvements in Aβ levels, the expression of α-synuclein, and SNCA levels in vivo and in vitro models after treatment. Regulation of these protein levels helps slow neurodegeneration and the buildup of plaques and proteins. In vivo and in vitro models have also been developed with CRISPR to test AD and PD treatments due to CRISPR's efficiency in cost and time. CRISPR is revolutionizing the process of gene editing and the field of medicine. However, there are still limitations that need to be acknowledged and solved when working with this technology. For example, off-target mutations and immunological responses by the body make it harder to implement this treatment in patients without safety concerns. More studies on the long-term effects of treatments need to be observed, and an efficient method of delivering CRISPR in vivo is in development.

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