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Gene Editing for the Treatment of Alzheimer's Disease: A Comprehensive Review

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by cognitive impairment, memory loss, and significant functional decline. Current treatment strategies focus on symptom management but do not target the disease's underlying genetic and molecular causes. Gene editing, particularly the CRISPR-Cas9 system, has emerged as a transformative tool to modify genetic pathways implicated in AD, including those related to amyloid-beta accumulation, tau hyperphosphorylation, and apolipoprotein E (APOE) polymorphisms. This review discusses the potential applications of gene editing in AD treatment, preclinical advancements, challenges in implementation, and the ethical considerations surrounding this innovative therapeutic strategy.

Introduction

Alzheimer's disease (AD) affects approximately 55 million people worldwide, making it the most prevalent form of dementia. Despite significant advancements in understanding its pathophysiology, no treatment effectively halts or reverses disease progression. Gene editing has emerged as a promising avenue, offering the potential to target genetic mutations and epigenetic modifications contributing to AD pathology. CRISPR-Cas9 and related technologies allow precise alterations to DNA and RNA sequences, enabling innovative approaches to address AD's genetic basis(1,2).

Genetics of Alzheimer's Disease

AD is classified into familial (early-onset) and sporadic (late-onset) forms. Familial AD is linked to autosomal dominant mutations in the *APP* (amyloid precursor protein), *PSEN1* (presenilin 1), and *PSEN2* (presenilin 2) genes. Sporadic AD, which accounts for over 90% of cases, has a complex etiology, with the *APOE* ε4 allele being the most significant genetic risk factor(3,4).

Key Genetic Targets in AD

- **Amyloid Precursor Protein (APP):** Mutations in *APP* increase amyloid-beta production, contributing to plaque deposition.
- **Presenilins (PSEN1 and PSEN2):** These genes encode components of the γ-secretase complex, which processes *APP*. Mutations enhance amyloid-beta formation.
- **APOE ε4 Allele:** *APOE* ε4 is associated with an increased risk of AD, while *APOE ε2* is protective. Modulating APOE expression or editing its variants holds therapeutic promise(4,5)

Gene Editing Techniques in AD Research

CRISPR-Cas9

CRISPR-Cas9 is the most widely used gene editing tool, capable of introducing targeted mutations, deletions, or corrections. Its potential applications in AD include:

- **Reducing Amyloid-Beta Levels:** Targeting *APP* and *BACE1* genes to lower amyloid-beta production(6).
- **APOE Modulation:** Editing the *APOE ε4* allele to convert it to the protective *APOE ε2* form.
- **Tau Pathology:** Suppressing genes responsible for tau hyperphosphorylation, a key feature of AD(7).

Base and Prime Editing

These techniques enable precise nucleotide changes without causing double-strand breaks. Base editing is particularly useful for correcting point mutations in *APP* and *PSEN1*, while prime editing allows for more complex genetic modifications(8).

Epigenome Editing

This method involves altering gene expression without modifying the DNA sequence. For example, CRISPR-based epigenetic tools can suppress genes involved in amyloid-beta production or enhance the expression of neuroprotective factors(9).

Preclinical Advances in Gene Editing for AD

Animal Models

Studies using mouse models of AD have demonstrated the efficacy of CRISPR in reducing amyloid plaques and improving cognitive function. For example, CRISPR-mediated knockdown of *APP* in transgenic mice led to a significant reduction in amyloid-beta accumulation(10,11).

Cellular Models

Induced pluripotent stem cells (iPSCs) derived from AD patients have been edited to correct *APP* and *PSEN1* mutations. These corrected cells show reduced amyloid-beta production and restored cellular function(12)

Challenges and Limitations

- **Delivery Systems:** Efficiently delivering gene editing tools to the brain is challenging due to the blood-brain barrier. Viral vectors (e.g., AAV) and

nanoparticles are being explored to enhance delivery(13).

- **Off-Target Effects:** Unintended genome edits can lead to harmful mutations. Improved specificity of gene editing tools is critical for clinical applications.
- **Ethical and Regulatory Concerns:** The use of gene editing in humans raises ethical questions, particularly regarding germline editing and equitable access to therapies.

Future Directions

Combining gene editing with other therapeutic modalities, such as immunotherapy and neuroprotection, may enhance treatment outcomes. Advances in delivery systems, along with next-generation gene editing tools like CRISPR-Cas12 and CRISPR-Cas13, are expected to improve safety and efficacy.

Conclusion

Gene editing offers a groundbreaking approach to tackling the genetic and molecular underpinnings of Alzheimer's disease. While significant challenges remain, ongoing research is paving the way for the development of curative therapies. Collaboration between scientists, clinicians, and ethicists will be essential to realize the full potential of gene editing in addressing this devastating disease.

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