Gene Therapy for Neurodegenerative Disorders

Abstract

Neurodegenerative diseases such as Alzheimer's and Parkinson's represent a significant and increasing health burden, indicated by progressive neuronal loss. Traditional treatments have limited effectiveness, often managing certain symptoms rather than stopping progression. Gene therapy, which involves modifying genetic material to treat or prevent disease, offers a promising path for addressing the causes of these disorders. This paper analyzes the potential use of gene therapy to revolutionize treatment for neurodegenerative diseases. We discuss the progression of these diseases, current treatment limitations, and the genetic factors involved. Despite its promises, gene therapy faces technical, safety, ethical, and accessibility challenges. While gene therapy can transform treatments for neurodegenerative diseases, obstacles may need to be overcome to utilize its full potential.

Introduction

Neurodegenerative diseases like Alzheimer's and Parkinson's affect millions of people worldwide, causing progressive deterioration of cognitive and motor functions as neurons in the brain degenerate over time. These devastating conditions have no cure, and current treatments can only slow their progression. According to leading expert Richard Armstrong, “In 2019, approximately 50 million individuals worldwide had a neurodegenerative disease often resulting in dementia, a number expected to rise to 152 million by 2060” (Armstrong). However, recent advances in gene therapy techniques promise to potentially treat or reverse neurodegenerative processes at the genetic level.

Gene therapy involves introducing genetic material into a patient's cells to neutralize abnormal genes or to make a beneficial protein (Paulo). For neurodegenerative diseases, this could mean sending genes that produce neuroprotective factors, replacing dysfunctional genes, or silencing genes that contribute to neurodegeneration.

While gene therapy shows immense potential to revolutionize the treatment of neurodegenerative disorders, significant challenges remain before it can become a clinical reality. As noted, these diseases involve complex interactions between multiple genes and environmental factors, making them difficult targets for gene therapy (Armstrong). Additionally, delivering genetic material to the brain effectively and ensuring long-term expression presents major technical limitations.

Understanding Neurodegenerative Diseases (AD)

Neurodegenerative diseases, particularly Alzheimer's disease (AD) and Parkinson's disease (PD), represent a growing global health crisis as populations age worldwide. These disorders cause the progressive loss of neurons in specific regions of the brain, leading to a decline in cognitive and motor functions.

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder affecting millions of people worldwide. As global life expectancy increases, AD is becoming an increasingly significant health and economic challenge. The disease typically begins with short-term memory loss and progresses to more severe symptoms. These include difficulties with language, disorientation, mood changes, and behavioral issues. In its advancing stages, AD leads to the loss of bodily functions and, ultimately, death. While age is the primary risk factor, it's important to note that AD is not an inevitable part of aging (Fish et al). Rare genetic mutations cause early-onset familial AD, accounting for a small percentage of cases. Additionally, other genetic factors, such as the apolipoprotein E4 (ApoE4) gene, can increase an individual's risk of developing the disease.

Two key features characterize the brains of individuals with AD: amyloid plaques that form outside brain cells, and neurofibrillary tangles that develop inside them. As the disease advances, the brain also experiences significant shrinkage due to the death of neurons (Fish et al). A 1992 study by researchers Hardy and Higgins states that the “deposition of amyloid β protein (AβP) is the causative agent of Alzheimer’s pathology and that neurofibrillary tangles, cell loss, vascular damage, and dementia

follow as a direct result of this deposition” (Fish et al). The "β-amyloid hypothesis" has long been central to AD research. This theory suggests that the accumulation of beta-amyloid protein in the brain is the primary cause of the disease. However, the role of tau protein tangles and their relationship with amyloid buildup is still not fully understood. Recent research also points to the potential importance of brain inflammation in the disease process.

Current treatments for AD are limited to managing symptoms, providing only subtle improvements in cognitive function. Ongoing research seeks to develop therapies that can slow or halt the progression of the disease. Most efforts target either the amyloid or tau proteins, though some researchers are exploring other approaches, including ways to reduce brain inflammation. Developing new treatments for AD has been challenging. Clinical trials are long and complicated, often lasting eighteen months or more. Measuring cognitive decline accurately is difficult as it is hard to assess the effectiveness of potential treatments.

Understanding Neurodegenerative Diseases (PD)

Parkinson's disease (PD) is a neurological disorder first described by Dr. James Parkinson in 1817. It primarily affects movement by causing symptoms like tremors, stiffness, slow motion, and balance problems. As people age, PD becomes more common, affecting about 1 in 100 people over 65. PD is caused by the loss of brain cells that produce dopamine, a vital chemical messenger. This loss occurs in a specific area of the brain called the substantia nigra. By the time symptoms appear, about 80% of these cells are already destroyed. scientists often find unusual clumps called Lewy bodies, which are a mixture of proteins and lipids, inside the remaining brain cells (Singh et al).

While the exact cause of PD remains unknown in most cases, researchers have identified several potentially causal factors: genetics, environment, and personality. Genetic mutations, toxin exposure, and risk taking, for example, may increase one’s risk of PD. Some studies suggest that smoking, caffeine, and even certain recreational drugs might lower the risk of PD (Singh et al).

Current treatments for PD focus on managing symptoms rather than curing the disease. The main approach is to replace or mimic the missing dopamine in the brain. This is typically done with medications like levodopa or dopamine agonists. However, these treatments often become less effective over time and can cause side effects.

The Basics of Gene Therapy

Gene therapy, a concept introduced 45 years ago, has emerged as a groundbreaking approach to treating various diseases. This medical technique involves introducing genetic material into cells to correct or replace faulty genes, potentially curing previously untreatable conditions.

The use of gene therapy has been marked by both triumphs and setbacks. A breakthrough came in 2000 when researchers successfully treated patients with severe combined immunodeficiency (SCID-X1) (Smith). However, early methods sometimes lead to unintended side effects, including leukemia in some patients. These challenges prompted the development of safer techniques.

The method of adding healthy genes introduces a functional copy of a gene to compensate for a defective one. It has shown promise in treating conditions like hemophilia and certain immune deficiencies. Gene editing techniques like CRISPR/Cas9 allow scientists to directly repair or modify faulty genes. This is important for treating dominant genetic disorders. The CART-T cell therapy form of gene therapy, primarily used for certain blood cancers, involves modifying a patient's immune cells to better target and fight cancer. The oligonucleotide therapy approach uses short sequences of DNA or RNA to interfere with gene expression or modify how genes are processed (Smith).

The vehicles used to deliver genes are called vectors (Wilson). These vectors must overcome several challenges: they need to target the right cells, penetrate them, reach the cell nucleus, and integrate the new genetic material into the cellular DNA. This process is far more complex than traditional drug delivery as genes are larger and negatively charged, making it difficult for them to cross cell membranes.

Early gene therapy techniques developed in the 1970s were inefficient but a breakthrough came in the 1980s with the idea of using modified viruses as vectors. There are two main types of viral vectors: retroviral and adenoviral. Retroviral vectors are based on mouse retroviruses and were the first to be used in humans. They can integrate genes into the cell's DNA, providing long-term gene expression. However, they can only infect dividing cells and have limited efficiency. Adenoviral vectors can infect non-dividing cells and achieve high levels of gene transfer. However, they often trigger immune responses, which can cause inflammation and limit their effectiveness (Wilson).

Potential for Gene Therapy in Neurodegenerative Diseases

CRISPR/Cas9 has been useful in studying neurodegenerative diseases. Recent developments in gene editing include techniques like “Base Editors” and “Prime Editors,” which allow for more precise genetic modifications without causing double-strand breaks in DNA (Zhu et al).

Three key genes associated with autosomal dominant AD have been identified: APP on chromosome 21, PSEN1 on chromosome 14, and PSEN2 on chromosome 1. These genes are involved in the production and processing of Aβ protein. Genome-wide association studies (GWAS) have revealed numerous risk loci, with ApoE4 being the most significant genetic risk factor for late-onset AD.

Some gene editing studies have focused on several areas: ApoE4, TREM2, APP, Presenilin genes, and Epigenetic factors. ApoE4 significantly increases AD risk. Researchers are exploring how ApoE4 affects aspects of cellular function, including neural differentiation and energy metabolism. TREM2, shared by both AD and PD, has been linked to microglial activation. In studies, TREM2-deleted mice have shown aggravated neurodegeneration. Researchers have successfully reduced Aβ generation in induced pluripotent stem cells by editing the C-terminus of APP using CRISPR. Studies have explored how phosphorylation of specific sites on APP can inhibit Aβ-related phenotypes. Studies on Presenilin genes have compared the effects of PSEN1 and PSEN2 mutations on Aβ accumulation, finding that PSEN2 mutations may lead to greater Aβ buildup. Touching on Epigenetic factors,, research in C. elegans

models has revealed how epigenetic modifications of proteins can affect age sensory decline and neuronal morphology (Zhu et al).

Genetic studies on PD have identified key genes including SNCA, PARKIN, LRRK2, P13, and DNAJC6. SNCA relates to α-synuclein expression and is a significant predictor for sporadic PD. Researchers have also developed CRISPR-based techniques to regulate SNCA transcription through methylation. PARKIN is involved in mitochondrial function regulation. Studies using CRISPR cell lines have investigated how mutations in these genes affect the expression of proteins and cellular responses to oxidative stress. Researchers have used gene editing techniques like TALEN to create models for studying LRRK2-related PD, providing valuable insights into disease mechanisms. Studies have shown that decreased expression of P13 can have protective effects in both genetic and toxin-induced models, while overexpression promotes PD phenotypes in mice. A DNAJC6 novel mutation in this gene was linked to early impairment in PD using human embryonic stem cell models (Zhu et al).

The future of gene editing research in AD and PD likely lies in combining these techniques with other cutting-edge technologies. This includes the use of advanced bioinformatics and machine learning to predict editing outcomes and the development of more sophisticated in-vitro models like brain organoids. Researchers are increasingly using computer science and bioinformatics to improve gene editing techniques and predict their effects more accurately. There's also a growing focus on understanding the common pathways shared by different neurodegenerative diseases, which could lead to more effective treatment strategies.

Gene editing tool	Vector	Disease	Target	Animal model	Injections	Results
CRISPR/Cas9	px330 plasmid	AD	App 3′-UTR	NL-G-F mice	Microinjected in mice zygotes	Deletion of App 3′-UTR mitigated Aβ pathology in the App KI mice.
CRISPR/Cas9	px330 plasmid	PD	p13 exon1	C57BL/6J mice	Injected into the pronuclear stage eggs	Heterozygous p13 knockout prevents motor deficits and loss of dopaminergic neurons in the substantia nigra.

TABLE 1. Studies of Gene Therapy for AD and PD (Zhu et al)

Ethical Concerns for Gene Therapy

CRISPR technology's potential applications are extensive and diverse. In agriculture, CRISPR could be used to create drought-resistant crops or enhance the nutritional value of food. In animal research, it could help develop more accurate models of human diseases. In medicine, it offers the opportunity to correct genetic defects and treat previously uncurable diseases. However, it's the potential application in human editing that has sparked an ethical debate.

One of the primary concerns with CRISPR/Cas9 is the potential for unintended changes in the genome. The technology might accidentally alter parts of the DNA that weren't targeted, potentially causing harmful effects that could be passed down to future generations. CRISPR/Cas9 is difficult to regulate effectively. There are concerns about potential misuse, especially given the international nature of scientific research and the varying regulatory frameworks across different countries. There are worries about using this technology for non-medical purposes, such as enhancing physical or cognitive traits. This raises questions about fairness, equality, and the nature of human identity. Ensuring the safety of patients in clinical applications is crucial, especially given the permanent and heritable nature of the modifications. Unlike other medical treatments, the effects of editing would be irreversible and could affect future generations. There are concerns about creating genetic inequalities, and there is potential for discrimination based on genetic modifications. If genetic enhancements become available, they might be accessible only to the wealthy, potentially exacerbating existing social inequalities (Shinwari).

Some researchers have called for a hiatus on genome editing until a broad social consensus can be reached. They argue that we need more time to fully understand the technology's implications and to develop appropriate regulatory frameworks. Others argue that regulated research should continue, as it could lead to significant medical breakthroughs. They point out that many genetic diseases cause suffering, and if we can prevent these conditions, we may have an ethical responsibility to do so.

As technology continues to advance, scientists, ethicists, policymakers, and the public need to communicate. This discussion should address not only the technical aspects of gene editing but also its

broader societal implications. It's crucial to consider diverse perspectives, including those from different cultural and religious backgrounds.

Conclusion

In conclusion, gene therapy has emerged as a promising treatment for neurodegenerative diseases like Alzheimer's and Parkinson's. The identification of key genes associated with these disorders, such as APP, PSEN1, and PSEN2 for Alzheimer's, and SNCA, PARKIN, and LRRK2 for Parkinson's, has opened new opportunities for targeted genetic interventions. Techniques like CRISPR/Cas9 and newer developments such as Base Editors and Prime Editors have expanded our ability to manipulate genetic material with precision. These tools have enabled researchers to explore important areas such as modifying the ApoE4 gene to reduce Alzheimer's risk, editing the C-terminus of APP to decrease Aβ protein generation, and regulating SNCA transcription in Parkinson's disease models.

However, the journey with clinical applications remains challenging and ethically complex. The studies involving complex neurodegenerative diseases, dealing with multiple genes and environmental factors, bring a thorough approach to gene therapy development. Moreover, the ethical implications of gene editing, particularly concerns about unintended consequences and potential misuse, demand careful consideration and regulation. As research in this field continues, it is important to maintain an open discussion among scientists, ethicists, policymakers, and the public to ensure that the development of gene therapies for neurodegenerative diseases proceeds responsibly, balancing the need for effective treatments to protect human health with societal values.

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