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A COMPREHENSIVE REVIEW OF NEW METHODS IN TREATMENT FOR NEURODEGENERATIVE DISEASES

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ABSTRACT :

Memory, thought, and movement are all impacted by the progressive loss of brain function brought on by neurodegenerative diseases (NDDs). The molecular causes of disorders like Parkinson's and Alzheimer's are examined in this overview, with particular attention paid to prion proteins and protein misfolding. Additionally, it talks about novel therapies that change gene expression and decrease the progression of disease, such as gene therapy and antisense oligonucleotides (ASOs). Particularly for Huntington's disease and amyotrophic lateral sclerosis, recent developments in ASO therapies and CRISPR/Cas9 gene editing hold promise. The review emphasizes the potential of new therapeutics to address the underlying causes of NDDs, but it also stresses the need for continued research to validate these approaches and resolve delivery issues to the brain.

Keywords: Neurodegenerative diseases, protein misfolding, antisense oligonucleotides, gene therapy, RNA and CRISPR/Cas9.

INTRODUCTION :

Millions of people worldwide suffer from neurodegenerative diseases (NDDs), which are a group of neurological conditions marked by a progressive loss of neurons in the vital central nervous system (CNS) or peripheral nervous system (PNS). Because neuronal networks are terminally differentiated, they are unable to successfully resume themselves as neurons die and neural networks lose structure and function. This disturbance affects the fundamental communication pathways, which undoubtedly leads to issues with behavior, memory, cognition, sensory perception, and/or motor skills.

The crucial processes of protein folding and misfolding establish a protein's role or placement inside the cell. For many active proteins to function correctly, they must form groupings, or oligomers. Complex systems made up of structural proteins like tubulin and actin are essential for a variety of cellular functions. Numerous cellular processes depend on the highly regulated creation of these groupings and systems. However, misfolded proteins can create dangerous, uncontrolled clusters that cause a number of illnesses. Protein misfolding disorders (PMDs), which include Alzheimer's disease (AD), Parkinson's disease (PD), and prion diseases, are age-related ailments caused by proteins that are normally folded correctly in the body but fail to do so.

It is known that nucleic acids (NAs) may interact with amyloidogenesis-prone proteins to promote the aggregation process. Multiple chemical contacts, including as hydrogen bonding mediated by water molecules, nonpolar interactions, and hydrophobic forces, are involved in the interactions between proteins and NAs.

METHODOLOGY :

Antisense Oligonucleotide treatments for Neurodegenerative issues

By changing the expression of mutant proteins, antisense oligonucleotides (ASOs) are used to modify RNA and protein expression, providing a calculated method to slow the progression of disease. Additional ASO therapies aimed at different illnesses of the central nervous system (CNS) have been made possible by the recent approval of ASO-based therapy for spinal muscular atrophy, a pediatric motor neuron ailment. Clinical studies for Huntington's disease (HD) and other neurodegenerative diseases have been made easier by developments in ASO chemistry and CNS delivery techniques. Among other neurological diseases, ongoing ASO-based clinical trials are also treating Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). In the near future, it is anticipated that ASO-based approaches will provide effective disease-modifying treatments for HD and related disorders.

ASOs use a variety of methods to alter gene expression. The recruitment of ribonuclease H1 (RNase H1) is one such mechanism. The ASO creates an RNA-DNA hybrid after attaching to the target RNA, which causes RNase H1 to degrade mRNA. ASOs can also bind to particular locations on target RNA to block ribosome attachment, which effectively prevents protein synthesis and translation. By lowering the amounts of harmful proteins, such as mutant huntingtin (mHTT) in Huntington's disease, superoxide dismutase 1 (SOD1) in ALS, and α-synuclein in Parkinson's disease, this method shows great promise in the treatment of neurodegenerative illnesses.

Gene therapy for Neurodegenerative issues

Many neurodegenerative diseases, including Parkinson's disease (PD), Canavan disease, spinal muscular atrophy, and Alzheimer's disease, have been investigated as potential treatments for gene addition. This technique entails the targeted delivery of cDNA for genes such as nerve growth factor (NGF), human aspartoacylase (ASPA), survival motor neuron (SMN), and AADC.

Given the great degree of protein similarity between rodents and humans, as well as their comparatively simple genomes, zinc finger proteins (ZFPs) are being investigated as possible therapeutic alternatives for neurodegenerative illnesses through gene editing and designed transcriptional regulators.

RNA interference (RNAi) is a potential method for silencing genes. For example, adeno-associated virus (AAV) injections of synthetic short hairpin RNAs (shRNAs) or microRNAs can provide more permanent gene silence than siRNAs, making them a more effective gene therapy strategy for neurological illnesses. A single dose of VY-HTT01 (Voyager Therapeutics) successfully decreased HTT levels in important nonhuman primate brain areas, according to preclinical research. Furthermore, mice models of Huntington's disease and spinocerebellar ataxia type 1 have demonstrated promise for AAV5-expressing microRNAs that target HTT and ataxin-1.

RNA-based therapies for Neurodegenerative illnesses

Because RNA-based therapies precisely regulate gene expression, they are becoming a promising therapeutic alternative for treating the problems linked to neurodegenerative disorders. These therapies may raise the amounts of proteins that are lacking or lower the levels of proteins that are detrimental. Through Watson-Crick base pairing, RNA treatments are designed to bind to their target RNAs selectively, allowing for targeted modification of the underlying molecular causes or important pathogenic mechanisms of diseases. The capacity of RNA-based therapeutics to directly target particular RNAs is a key benefit. This broadens the pool of possible therapeutic targets beyond what is available with conventional medications, which are usually restricted to small molecules or antibodies. Antisense oligonucleotides (ASOs) and RNA interference (RNAi) are the two main categories into which RNA therapies are typically divided.

CRISPR/Cas9 as a singular healing for neurodegenerative diseases

The groundbreaking genome-editing technique CRISPR/Cas9 has greatly revolutionized biological research. Scientists have discovered that these repeats are usually located next to clusters of CRISPR-associated (Cas) genes. Numerous animals, including human tripronuclear zygotes and non-human primates, have shown evidence of using CRISPR/Cas9 to modify their genomes. In addition to germline editing, CRISPR/Cas9 may target genes in somatic tissues, including brain neurons. Degeneration of dopaminergic neurons in the substantia nigra is a major pathogenic characteristic of Parkinson's disease (PD). Researchers can examine the consequences of gene loss, like that of Parkin or Pink1, on Parkinson's disease pathology by using viral systems to deliver gRNAs and Cas9 to the substantia nigra in animal models. This method is especially useful for examining neurological alterations brought on by aging. Additionally, CRISPR/Cas9 can create knock-in mutations to create animal models of diseases brought on by hazardous gain-of-function mutations, such Huntington's disease (HD) from polyglutamine (polyQ) expansion in huntingtin or Parkinson's disease (PD) from α-synuclein mutations. Researchers may create models that correctly reflect these disorders by co-injecting Cas9/gRNAs with donor DNA that contains mutant sequences. This allows them to replace the endogenous gene with the defective one.

CURRENT TENDENCIES AND MEDICAL TRIALS :

1. **Amyotrophic lateral sclerosis (ALS):** Antisense oligonucleotides (ASOs) have made significant progress in treating mutations in the SOD1 gene, which results in familial ALS. The FDA approved Tofersen, an ASO that inhibits the mutant SOD1 protein, in 2020. Other approaches, like as gene silencing and RNAi-based therapies targeted targeting TDP-43, are also being investigated.

2. **Huntington's ailment:** A mutation in the HTT gene leads to the creation of a toxic protein that harms neurons, which is the cause of Huntington's disease. Preclinical models have demonstrated that RNA-based treatments, such as gene silencing with antisense oligonucleotides (ASOs), decrease the production of the mutant huntingtin protein. Clinical trials are under underway to find treatments that could potentially stop or delay the progression of the disease.

3. **Alzheimer's ailment:** The accumulation of tau tangles and amyloid-beta plaques is a hallmark of Alzheimer's disease. Targeting the genes that produce tau or amyloid precursor protein (APP) has been the goal of gene-based approaches in Alzheimer's research. But when it comes to getting nucleic acid treatments into the brain, the blood-brain barrier (BBB) remains a significant obstacle.

4. **Parkinson's disorder:** When dopamine-producing neurons begin to deteriorate, Parkinson's disease results. Nucleic acid therapies, particularly gene therapies that provide dopamine-producing enzymes like AADC (aromatic L-amino acid decarboxylase), are being investigated by researchers. Additionally, they are developing RNA-based therapies that target the protein alpha-synuclein, which causes poisonous clusters in Parkinson's disease.

RESULT :

Memory, thought, behavior, and movement are all affected by the progressive loss of neurons that characterizes neurodegenerative diseases (NDDs). This typically occurs when proteins misfold and group together, such as mutant huntingtin in Huntington's disease, β-amyloid in Alzheimer's disease, and α-synuclein in Parkinson's disease. Emerging therapies that target the underlying causes of these illnesses include CRISPR/Cas9, RNA interference (RNAi), and antisense oligonucleotides (ASOs). ASOs, such as IONIS-HTTRx, have demonstrated significant promise in the treatment of Huntington's disease (HD); a recent study found that injections of ASOs into spinal fluid resulted in dose-dependent decreases in mutant huntingtin (HTT). Numerous

new therapy options are made possible by these RNA-based medicines' ability to precisely regulate protein and RNA levels. Furthermore, precise gene editing is possible with CRISPR/Cas9, enabling targeted modifications to the genes causing disorders like Huntington's and Parkinson's. These developments in gene and RNA therapeutics present encouraging approaches to treating illnesses and enhancing patient outcomes.

CONCLUSION :

There is hope for tackling the intricate molecular pathways behind neurodegenerative illnesses thanks to emerging therapeutics including CRISPR/Cas9, gene therapy, RNA-based treatments, and ASOs. By offering alternatives for disease modification and enhancing patient outcomes, these strategies have the potential to completely change the therapy landscape.

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