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USE OF GENE THERAPY IN THE TREATMENT OF ALZHEIMER'S DISEASE – LITERATURE REVIEW

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ABSTRACT

Neurodegenerative diseases are the most common cause of dementia, affecting around 55 million elderly worldwide, Alzheimer's Disease (AD) corresponds to 60% of all cases. These elderlies reveal memory loss, impairment of language and thought formulation. AD has no cure, only its symptoms are treated, which does not prevent the disease from progressing. Also, throughout the course of brain degeneration progress, drugs no longer show significant effects. For this reason, the set of changes in the DNA of individuals who suffer from the disease can provide an important biomarker that has been the target of studies involving gene therapy. This technique occurs through the correction of modified genes or site-specific modifications, which can be through DNA or RNA, intending to treat or prevent diseases and uses a viral or non-viral vector which helps deliver genetic material to the cell.

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In the following we searched for clinical studies that portrayed some advances in the treatment of AD using gene therapy techniques. Due to the ability to alter and induce the expression of specific proteins, gene therapy presents a promising future in the restoration and correction of the pathogenic mechanism.

Keywords: Alzheimer. Gene Correction. Gene Therapy.

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INTRODUCTION

Neurodegenerative diseases affect around 55 million people worldwide (ADI, 2020). Among them, Alzheimer's disease (AD) accounts for 60% of all cases, being the most common form of dementia among the elderly and is defined as a progressive brain degeneration that reduces mental capacity due to the death of cortical neurons (GAUTHIER et al., 2021).

The pathogenesis of this disease involves the accumulation of β-amyloid protein plaques between neurons, which prevents neuronal transmission. The excess of this peptide is suggested by a polymorphism in the apoE gene, which, in the brain, is responsible for regulating the aggregation and clearance of β-amyloid. Another important biomarker is the hyperphosphorylated TAU protein that affects biological and morphological functions in neurons (ROBINSON et al., 2018).

The onset of AD occurs in the hippocampus and progresses to other brain areas. Therefore, patients suffering from this disease experience chronic and progressive memory loss, language impairment, disorientation, impaired visuospatial function and aggressive behavior in the more advanced stages of the disease, which also causes suffering to family and friends.

AD has no cure and currently available treatments only alleviate symptoms, but do not prevent the disease from progressing. As brain degeneration progresses, drugs no longer show significant effects (SUDHAKAR; RICHARDSON, 2019).

Thus, gene therapy has been the subject of studies for the treatment of Alzheimer's disease for some years. This technique occurs through the correction of mutated genes or site-specific modifications, which can be through DNA or RNA and using a viral or non-viral vector that helps deliver the corrected genetic material to the cell.

The present study deals with a literature review about some publications located in periodicals. The data collected were made with possible conclusions from several authors with the aim of assisting in the study of gene alterations through gene therapy for the future treatment of Alzheimer's Disease.

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LITERATURE REVIEW

ALZHEIMER'S DISEASE

Neurodegenerative diseases are the most common cause of dementia, with Alzheimer's disease (AD) being the most prevalent. Around 50 million people live with AD and this number could exceed 70 million by 2030 (ADI, 2020).

AD can be divided into early-onset AD (FAD- Familial Alzheimer's Disease) and late-onset AD (LOAD- Late Onset Alzheimer's Disease). FAD has autosomal dominant inheritance and occurs before the age of 60. This form is less common, accounting for 1% to 6% of cases. LOAD is the most common form of Alzheimer's disease and has a late onset, over the age of 60. The cause of LOAD is not yet well defined, but it may be related to genetic components, such as the Apolipoprotein E (APOE) gene, and environmental components, such as aging. Both FAD and LOAD have the same pathology that constitutes an accumulation of dysfunctional proteins in the brain. The clinic is also the same, where patients deal with loss of memory and cognitive function (BEKRIS et al., 2010).

The pathophysiology of AD is characterized by the formation of beta-amyloid protein plaques and neurofibrillary tangles of hyperphosphorylated TAU protein. This accumulation leads to neuronal death and loss of synaptic connection between neurons, which initially occurs in the hippocampus and then spreads to other brain regions. For this reason, patients with AD experience memory loss, impaired language and thought formulation (KHAN; BARVE; KUMAR, 2020).

The neuroinflammation that these proteins cause contributes to the degradation of neurons in the nucleus basalis of Meynert, the place where neurons that use acetylcholine as a neurotransmitter project throughout the cortex. Therefore, acetylcholine deficit impairs cognition. It also alters the permeability of the blood-brain barrier, causing erroneous transport of metabolites and making it difficult to remove the amyloid plaque, worsening the disease condition (HAMPEL et al., 2018).

BETA-AMYLOID PLAQUES

The difficulty in synaptic connection is explained by the accumulation of beta-amyloid (Aβ) protein plaques between neurons. These plaques are recognized as foreign material by the brain, generating an inflammatory and immunological response that leads to the death of neurons (KHAN; BARVE; KUMAR, 2020).

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Acute inflammation has a protective role in defending against brain injuries, such as the presence of Aβ plaque. However, the continuous activation of microglia makes it impossible to remove this plaque, decreasing the ability to release pro-inflammatory cytokines which results in an imbalance between pro- and anti-inflammatory cytokines. Beta-amyloid deposits activate several Toll-like receptors such as TLR2, TLR4, and TLR6 as well as their coreceptors, including CD36, CD14, and CD47 expressed by microglia. Upon detection of microorganisms, pro-inflammatory cytokines are produced by the immune system, including the cytokine IL-1β and IL-18. These pro-inflammatory cytokines can impair dendritic spines and disrupt microglial Aβ clearance. When encountering pro-inflammatory cytokines, neurons and glial cells express inducible isoforms of NO synthase, which increases the synthesis of nitric oxide (NO). This increases the peptide's ability to aggregate and makes it more potent in synapse suppression (HENEKA; GOLENBOCK; LATZ, 2015).

The beta-amyloid peptide originates from the amyloid precursor protein (APP), which is a transmembrane glycoprotein. The function of Aβ is not known for certain, however, it is believed that it contributes to the formation of synapses and dendritic and axonal growth. APP undergoes proteolytic processing through the action of alpha (α), beta (β) and gamma (γ) proteases. Thus, several peptides are formed that exhibit different aggregation potentials and different levels of toxicity. There are several forms of Aβ, which can be Aβ 34, Aβ 40, Aβ 42. Although Aβ 40 is the most abundant physiological form, Aβ 42 is the most important for the accumulation of beta-amyloid in the brain (HARDY; SELKOE, 2002).

TAU PROTEIN

Tau proteins are microtubular neuronal proteins. They have a microtubule-binding domain that acts to stabilize the assembly of microtubules while maintaining the integrity of the cytoskeleton. This binding is regulated by a variety of kinases such as cyclin-dependent kinase-5 (CDK5). CDK5 contributes to the formation of neurofibrillary tangles. Beta-amyloid activates calpain and deregulates p35, which is an activator of CDK5. Due to calcium overload in the cytosol, p35 divides into p25, which hyperactivates CDK5 and leads to tau hyperphosphorylation (CREWS; ROCKENSTEIN; MASLIAH, 2009).

Hyperphosphorylation results in decreased affinity of tau proteins for microtubules. This may occur due to a mutation in the tau genes or the deregulation of the kinases and phosphatases that catalyze phosphorylation. Hyperphosphorylated tau is deposited in the

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cytosol and loses its function of maintaining the cell structure. This deposition impairs synaptic transmission, axonal transport and signal transduction, causing the cell to gradually degenerate (HUANG et al., 2019).

APOLIPOPROTEIN E

Excess beta-amyloid is suggested by a polymorphism in the APOE gene, which, in the brain, is responsible for regulating the aggregation and clearance of beta-amyloid. Also, this gene leads to the presence of neurofibrillary tangles of hyperphosphorylated TAU protein (ROBINSON et al., 2018).

The APOE gene encodes glycoprotein present in the brain, liver, monocytes and macrophages. It is involved in neuronal growth, nerve regeneration, and the repair response to tissue injury. Furthermore, it participates in cholesterol transport, immunoregulation, and the activation of lipolytic enzymes. It contains three main allelic variants in a single gene locus, namely ε2, ε3 and ε4, which encodes different ApoE2, ApoE3 and ApoE4 isoforms. APOE4 increases the risk of FAD and LOAD, but is not sufficient to cause AD. The risk of developing the disease increases three times for heterozygotes and 15 times for homozygotes. About 20-25% of the general population carries one or more ε4 alleles, where 40-65% of AD patients are ε4 carriers. The APOE ε2 allele may have a protective effect and delay the age of onset (VAN CAUWENBERGHE; VAN BROECKHOVEN; SLEEGERS, 2016).

APOE binds to amyloid peptide and effects the clearance of soluble Aβ and Aβ aggregations. The APOE4 allele has been associated with increased vascular and brain parenchymal amyloid burden as it is less efficient in mediating Aβ clearance. Also, APOE4 showed a greater disruptive effect than APOE3 and APOE2 when interrupting beta-amyloid clearance across the BBB in mice. However, it is still unclear how APOE isoforms influence this accumulation of Aβ in the brain (DEANE et al., 2008).

GENE THERAPY

Gene therapy emerges as an alternative for the treatment of diseases that do not yet have a cure and for which pharmacological treatments no longer have any effect. This therapy consists of a set of techniques that use DNA or RNA to correct a disease. These nucleic acids are introduced into target cells to modulate non-functional proteins. There are different strategies that can be used, such as: introducing a functional copy of a defective

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gene, silencing a mutant allele, introducing a disease-modifying gene or using gene editing methods (SARAIVA; NOBRE; PEREIRA, 2016).

In the case of Alzheimer's disease, the progressive accumulation of dysfunctional proteins such as beta-amyloid leads to cell death. There are no existing medications that correct this process, only symptomatic relief, which does not prevent the progression of the disease. As the disease progresses, the effectiveness of pharmacological treatments is also reduced, increasing side effects. Also, due to the blood-brain barrier (BBB), significant amounts of these systematically administered drugs cannot reach the brain parenchyma and reach therapeutic levels without producing toxicity. Therefore, as the dosage of the medication increases, side effects also increase (RICHARDSON et al., 2009).

As a result, gene therapy emerges as a promising alternative for the treatment of neurodegenerative diseases such as AD. Because it is administered in a direct intracerebral neurosurgical manner, this technique bypasses the BBB, reaching the disease process with functional-anatomical specificity, avoiding exposure to other brain areas in which transgene expression is not necessary or unwanted. Some therapeutic molecules can be administered directly into the brain parenchyma or the genes that encode these types of molecules can be administered. When molecules are used, chronic infusion of the therapeutic agent is required, while a single gene therapy infusion may last for a decade or more (RICHARDSON et al., 2009).

Treatment using gene therapy depends on the pathogenesis of the disease and the temporal evolution of the pathological phenotype. Also, the temporal and spatial specificity of gene expression must be considered. Temporal specificity in gene therapy is due to constitutive (genes expressed in all cell types) or regulated (genes specific to one cell type) gene expression, while spatial specificity is due to how gene expression is confined to a specific brain region or cell type (RICHARDSON et al., 2009).

The CNS gene therapy approach depends largely on the delivery system selected. Non-viral vectors such as liposomes, exosomes, polymeric nanoparticles are an option, as they are simple and economical to produce. However, they have low efficiency and require repeated administrations, leading to the risk of triggering an immune response. Therefore, recombinant viral vectors constitute the most efficient system to achieve stable and long-term gene expression in the CNS. The vectors of choice for gene transfer to the CNS are adeno-associated viruses (AAV) and lentiviruses (SARAIVA; NOBRE; PEREIRA, 2016).

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Gene Therapy can be divided into two types: in vivo and ex vivo therapy. In the in vivo approach, the gene of interest (transgene) is introduced directly into the target region using viral vectors. It is considered more efficient and less expensive. However, in vivo therapy may have some complications such as vector-directed immune responses, low degree of specificity and control of gene transfer and insertional mutagenesis (MINGOZZI; HIGH, 2011).

AAV vectors are preferred for in vivo gene therapy. These viruses have relatively low immunogenicity, ability to transduce dividing and quiescent cells, in vivo transduction efficiency, long-term transgene expression in quiescent cells, tropism for specific tissues and cell types such as neuronal tissue, non-pathogenicity, and a history of clinical safety (LI et al., 2023).

In *ex vivo* gene therapy, cells are modified to produce therapeutic factors before being transplanted into the patient. This transplant can be done autologously and the main vectors used are lentiviruses (LI et al., 2023).

For CNS pathologies, an LV vector is used for in vitro genetic modification of hematopoietic stem cells (HSCs) isolated for genetic modification. These cells are later transplanted and become part of the bone marrow stem cells. In this way, some of these cells can migrate towards the CNS and cross the BBB and can differentiate into microglia, astrocytes or oligodendrocytes aiming to restore the normal functions of neurons. However, this method is highly complex and time-consuming, has a low survival rate of transplanted cells and the possibility of generating immunosuppression (PIGUET; ALVES; CARTIER, 2017).

The problem with gene therapy based on LV vectors is the generation of replication-competent viruses, as LV vectors normally insert themselves into the host's DNA, insertional mutagenesis that can lead to cancer, mobilization of the vector by endogenous retroviruses in the genomes of patients, alteration of the germline resulting in transgenerational effects and dissemination of new viruses from patients undergoing gene therapy (CONNOLLY, 2002).

ADENO-ASSOCIATED VIRUSES

Adeno-associated viruses (AAVs) are the most important and safe gene delivery vectors in the field of gene therapy. They belong to the Parvoviridae family made up of the smallest single-stranded deoxyribonucleic acid (DNA) (ssDNA) viruses. They have a non-

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enveloped icosahedral capsid, small size (18 to 26 nm) and a limited genetic repertoire where their genome is composed of three replication genes (Rep), capsid structural genes (Cap or VP1, -2 and -3) and associated genes the assembly (AAP) (GRIEGER; SAMULSKI, 2012).

These viruses can be subdivided into serotypes based on their capsid profiles. Viral vector particles are transported within the brain from one region to another, either anterograde (transduction of cells in a region of the brain that receives projections from the infusion site), retrograde (transduction of cells in a region of the brain which sends projections to the injection site) or both (SALEGIO et al., 2012).

Also, AAVs are dependent on a helper virus, usually an adenovirus, to replicate and are therefore part of the Dependovirus genus. Due to this, it makes them more dependent on a host cell than any other DNA virus and therefore they are not pathogenic. Due to these characteristics, as well as their strong neuronal tropism, long-term gene expression, low capacity to integrate genomes into the host chromosome, transduction of dividing and non-dividing cells, genetically modified dependent viruses are excellent candidates for use in therapy. gene (GRIEGER; SAMULSKI, 2012).

LENTIVIRUS

Lentiviruses (LV) belong to the retrovirus genus. They are spherical-shaped particles with a diameter of approximately 100 nm and contain a diploid genome with two positive-sense, single-stranded RNA molecules. These viruses present stable expression of the transgene for long periods and infect cells by integrating the genome into the target cell (CAVALIERI; BAIAMONTE; LOIACONO, 2018).

For this reason, despite being used in gene therapy for CNS disorders, LV are not the most recommended as they have a risk of insertional mutagenesis that can lead to cancer. Also, other concerns associated with this vector include the possible generation of replication-competent lentiviruses during vector production, mobilization of the vector by endogenous retroviruses in patient genomes, germline alteration resulting in transgenerational effects, and dissemination of new viruses from patients in gene therapy (CONNOLLY, 2002).

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AUTOPHAGY

Recently, autophagy has been implicated in neurodegeneration. However, it is not known for sure whether it is harmful or protective. Autophagy is the main cellular pathway for degradation of long-lived proteins and organelles and regulates cell fate in response to stress. A 2008 study showed that the protein beclin 1, present in the autophagy process, was decreased in affected brain regions of AD patients early in the disease process. Also, heterozygous deletion of beclin 1 in transgenic mice expressing human amyloid precursor protein (APP) decreased neuronal autophagy resulting in increased extracellular and intraneuronal deposition of Aβ causing neurodegeneration, lysosome disruption, microglial changes and profound structural abnormalities of neurons. (PICKFORD et al., 2008).

After administration of a lentiviral vector that expresses beclin 1, there was a decrease in intracellular and extracellular amyloid pathology in transgenic mice. Thus, it was concluded that increased levels of beclin 1 may have therapeutic potential in AD, as the deficiency of this protein interrupts neuronal autophagy and modifies APP metabolism resulting in neurodegeneration in mice (PICKFORD et al., 2008).

AMYLOID PEPTIDE

A 2018 study showed promising results for early-stage AD. Targeting amyloid peptide aggregates, it generates a human monoclonal antibody, Aducanumab. In the PRIME study involving patients with AD, aducanumab was shown to penetrate the brain, bind to parenchymal Aβ and reduce levels of soluble and insoluble Aβ and decrease brain TAU levels in a time- and dose-dependent manner, conferring clinical benefit. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduced brain Aβ in a dose- and time-dependent manner accompanied by a slowing of clinical decline as measured by Clinical Assessment Scale scores. Dementia (CDR- Clinical Dementia Rating) and Mini Mental State Examination (MMSE) (SEVIGNY et al., 2018).

In 2021, the Food and Drug Administration (FDA), the agency responsible for regulating medications and foods in the United States, approved Aducanumab from the pharmaceutical company Biogen. However, there is controversy regarding the use of aducanumab, as it has not been unanimously approved by the FDA. The committee made up of researchers, doctors and biostatisticians did not consider that the tests were effective in treating the disease. Despite this, Aducanumab proved to be the most promising drug for AD in the last decade (TEIXEIRA et al., 2023).

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In 2020, a study showed that high levels of CD33, a sialic acid-binding transmembrane receptor on the surface of microglial cells, inhibits the uptake and clearance of beta-amyloid. CD33 is present in microglial cells from brains of post-mortem AD patients, and high levels of CD33 inhibit the uptake and clearance of beta-amyloid (Aβ) in microglial cell cultures (GRICIUC et al., 2020).

This study used an intracerebroventricular injection of an adeno-associated virus (AAV) vector-based system encoding an artificial microRNA targeting CD33 (CD33miR) into transgenic AD mice (APP/PS1). Knockout of CD33 reduced the mRNA levels of CD33 and soluble Aβ40 and Aβ42 in brain extracts. Treatment of APP/PS1 mice with CD33 miR vector at the age of 2 months was found to be more effective in reducing Aβ plaque burden than at later time points (8 months). Also, this early intervention decreased pro-inflammatory activation genes (e.g., Tlr4 and Il1b) and reduced the pro-inflammatory cytokine TNF-alpha. Thus, CD33 is a viable target for future AAV-based therapies to reduce AD pathology (GRICIUC et al., 2020).

CONCLUSIONS

According to the above, the biggest target for gene therapy tests for the treatment of AD are beta-amyloid peptide aggregates. This is because the accumulation of Aβ between neurons prevents the formation of synapses and generates an inflammatory response that degenerates neuronal cells. Thus, advances in knowledge of the pathophysiology of AD have made it possible to identify new therapeutic targets. Considering the articles reviewed, gene therapy has enormous potential to prevent the progression or even cure Alzheimer's disease. However, despite successful clinical trials that showed a reduction in the pathogenic mechanism of AD, gene therapy techniques for the treatment of AD still face challenges requiring further improvement and investment aimed at consolidating them as a viable treatment in the future.

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