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REVIEW ARTICLE

Pathophysiologic Alteration of Alzheimer's Disease

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ABSTRACT
Alzheimer's disease (AD) pathogenesis involves Aβ accumulation due to imbalances in formation and elimination. Genetic treatment, utilising Aβ- degrading enzymes, emerges as a promising alternative, offering enhanced security through novel viral vectors. Unlike small chemical therapies, gene therapy facilitates the up-regulation of critical enzymes in AD. Ex vivo trials show promise, but the focus shifts to in vivo techniques for efficiency. Safety, optimal gene dosage, and precise expression targeting are pivotal. Ongoing exploration of viral vectors aims for refined specificity, including switchable systems like tetracycline. While disease-modifying AD medicines show modest results, gene technologies targeting specific brain areas in animals unveil potential therapeutic pathways. Development hinges on understanding disease courses, biological endpoints, and patient group selection. Genetic treatment, designed for targeted brain areas, holds promise in the fight against AD, shedding light on neural network impacts and disease physiopathology. In the intricate AD landscape, genetic therapy stands as an innovative approach, intertwining scientific advancements with a deeper comprehension of this debilitating condition.
KEYWORDS:- *Alzheimer's disease, Therapeutic strategies, Target candidate for gene therapy*

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INTRODUCTION

Alzheimer's disease (AD), which is the most common serious neurological illness, represents a chronic neurological illness marked by memory problems and a reduction in cognitive abilities. Major neuropathological indicators of AD include extracellular plaques containing amyloid and intracellular buildup of increased phosphorylation Tau protein, the microtubule assembling proteins, which results in neurofibrillary knots (NFTs)[1]. Dystrophic neurites typically surround symbols, which are made of up amyloid peptides produced by the breakdown of the APP [2]. Reactive astrogliosis, plaques, and the degeneration of synapses and neurons are all related. Although the exact processes behind these neuro-pathological alterations are unknown, a mix of hereditary and external factors are likely to be to blame.

Gene therapy for neurological conditions has progressed clearly during the previous few years. Numerous advancements in fundamental technologies, such as the discovery of novel therapeutic targets and new vectors, have been made possible by increasing awareness of the pathogenetic processes underlying these diseases1[3]. As an outcome of the improved understanding, various genetic medicines have remarkably addressed the fundamental causes of neurological conditions with both single-gene as well as complicated etiologies. The received, even long-lasting therapeutic effects of genetic therapy are especially appealing for separating organs like the retina, the cochlea, or the central nervous system (CNS), whose structures are difficult to treat because most medications can't breach physical barriers like blood-retinal barrier (BRB), the blood-cerebrospinal fluid barrier (BCSFB) and blood-brain barrier (BBB) [4]. Genetic therapy may also be capable of addressing some biological problems that are difficult to treat with traditional medications since it can handle both the silence of genes for dealing with the gain of function changes and genetic over-expression to manage the loss of functional abnormalities. specific biological targets that are hard to address with traditional medicines [5].

Genetic therapy for neurological disorders has been tested in several clinical studies [6]. Possibly as a result of poor biological distribution inside their designated tissues, many initial clinical trials failed to

provide appropriate medical results. Gene treatments have demonstrated expanded transgene expression and therapeutic safety because of advancements in AAVs and non-viral delivery techniques [7]. It's important to highlight that animal models on several neurological conditions, Parkinson's disease (PD), including Huntington's disease (HD), and a loss of the enzyme aromatic-L- amino-acid decarboxylase (AADC), have recently demonstrated excellent functional outcomes [8].

DISEASE GENESIS OF AD

Pathogenic characteristics of the brain affected by AD include plaques containing amyloid and neurofibrillary knots (NFTs), which are generated by a buildup of exterior amyloid 1-peptide (Aβ) and interior hyperphosphorylated tau, respectively [9]. Even though the deterioration process may start long before the first clinical indications appear, a dramatic loss of neurons and synapses is also seen, along with ventricle enlargements, and this condition is linked to clinically recognized cognitive impairment [10].

Aβ is created by the serial proteolytic breakdown of a type I membrane protein called the ancestor of amyloid (APP) by the β-secretase enzymes and β-secretase (1-site APP-cleaving enzyme 1, BACE1), which is made up of nicastrin, Pen- 2, Aph-1, and presenilin (PSEN), nicastrin. A soluble N-terminal fragment (βAPP) and a membrane-bound C-terminal fragment (CTF-1) are produced by the breakdown of each APP by β-secretase. CTF-1 is then further broken down by l'-βsecretase to produce the 40–43 amino acids that make up protein Aβ. Nearly all cells contain APP, which has undergone little change over development and has significant expression in brain cells. Although several investigations have revealed that APP possesses neuroprotective or neurotrophic activities, its physiological significance is still unclear. Early-onset familial AD (FAD) has been linked to genes encoding PSEN1, PSEN2, and APP. The inherited mode of transmission of mutations in these genes associated with FAD causes aggressive disease and raises either the overall level of Aβ or the ratio of Aβ 42/Aβ 40. Compared to Aβ 40, Aβ 42 is more hydrophobic and prone to agglomerate. These findings strongly suggest a causal connection between the pathophysiology of AD and the Aβ accumulation [11]. However, plaques of amyloid may not always be the primary factor causing synapse loss, death of neuronal cells, and ultimately brain shrinkage in AD [12].

There is proof that the main pathogenic organism impairing synapse and neural activities is aqueous A-oligomers, not plaques of amyloid [13]. For instance, it has been demonstrated that Aβ oligomers are very toxic, inhibit LTP, cause synapse retractions, and damage the ability to remember and think. On the opposite hand, plaques containing amyloid (Aβ fibrils) promote the proliferation and activation of glial cells, which causes the release of toxic chemicals. This suggests that they may indirectly contribute to neural malfunction. The neurological disorders have not been replicated in any of the genetic mice models that collect oligomers of Aβ and Aβ plaques, hence none of the hypotheses can be regarded experimentally verified. It was just demonstrated that Aβ43 and other extracellular plaque components seen in brains with Alzheimer's may also lead to aggregation. According to recent research, Aβ can connect to certain receptors and induce neuropathology when it binds to cellular prion proteins or the a7 nicotinic acetylcholine receptor (a7nAChR), further supporting the idea that Aβ plays a pathogenic part in AD. There is compelling evidence that dependence on concentration accumulation constitutes among the main root causes of Alzheimer's Disease. However, additional parts such as APOE-associated lipid metabolism, elevated tau phosphorylation, and inflammation are also likely to be involved. Greater stable state levels of Aβ may be the consequence of both increased production and lower breakdown of Aβ, which is continually processed in the brain. The endothelin-converting enzyme (ECE), neprilysin, cathepsin B, matrix metalloproteinases, the insulin-degrading enzyme (IDE), the endothelin-converting enzyme (ECE), plasmin, and the ACE (angiotensin-converting enzyme) have all been linked to the breakdown of Aβ. Neprilysin has been identified as one of these proteases that is primarily responsible for destroying Aβ, with ECE and IDE having less of an impact. The Aβ-degrading enzyme could be the focus of Aβ-lowering therapies, such as gene therapy strategies that attempt to increase Aβ-degrading activity.

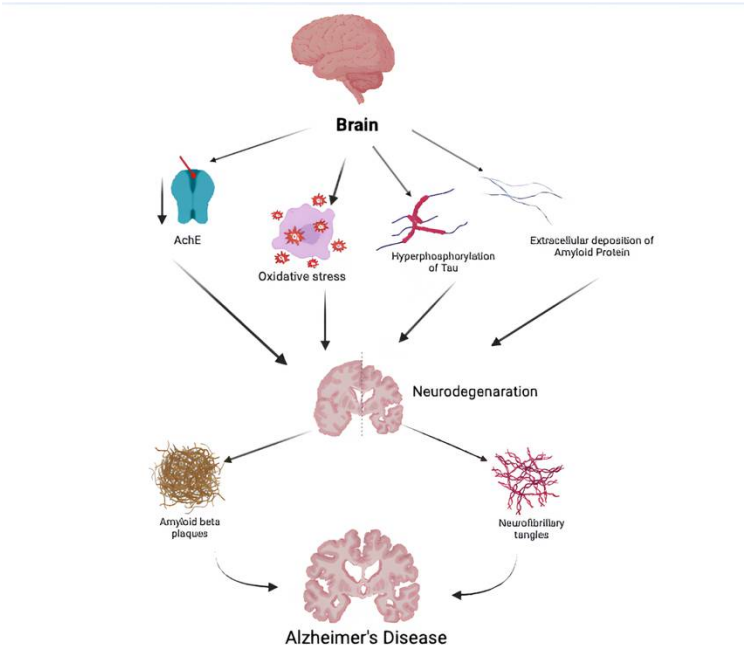

Fig.1 **Pathophysiology of Alzheimer Disease.**
Various etiopathogenesis of AD resulting the formation of Aβ plaques, NF Tangles.

All possible options for therapy should be taken into account considering the rising prevalence of people with AD, the rising expenses of Alzheimer's medical care, and last yet not least, the human suffering of patients and their carers [14]. The only anti-dementia medications now on the market are acetylcholinesterase inhibitors (AChE) like rivastigmine, galantamine, and donepezil, as well as an NMDA antagonist called memantine. Sadly, they only briefly improve the symptoms and do not halt the disease's development. However, therapy employing the Aβ-vaccine has produced some encouraging disease-modifying benefits, and several clinical trials are currently underway. Additionally, a growing body of research has demonstrated the effectiveness of genetic therapy in treating several illnesses, including AD. Genetic treatment offers the ability to compensate for very low levels of bioactive compounds by directly increasing enzyme activity. This is done by introducing a transgenic creature via a vector, usually an infectious agent that attacks the host cells and causes the gene to be expressed there. The treatment of numerous neurological and neurological illnesses with gene therapy has proven successful. More than 1340 clinical studies targeting more than 100 genes are currently allowed for a range of illnesses, largely cancer-related, in 28 different countries [15]. Due to concerns about the security of using viral vectors for transmission, gene therapy momentarily experienced a delay. For instance, during a clinical conduct of retrovirus-based genetic therapy for X-linked serious combined immunodeficiency, the augmenting vector's genome was injected near an LMO2 promoter, resulting in leukaemia in five patients, one of whom passed away. Such instances are uncommon, though, and there have been several successful experiments. For instance, metastatic melanoma and chronic granulomatous illness have both been treated by retroviral vector-mediated gene delivery employing gene-transfected T cells and stem cells from the bloodstream, respectively.

THERAPEUTICAL STRATEGIES FOR ALZHEIMER'S DISEASE

Acting directly on APP metabolism

Reducing the amyloid route by inhibiting secretase activity. Anti-BACE1: Given that BACE1 is essential for the generation of Ab, it is a clear therapeutic target [16]. BACE1 inhibitors of small molecules have been developed, and several of them are now through various phases of clinical studies. By employing lentiviral vectors that produce siRNA, the amyloid accumulation, neurodegeneration, and aberrant behavior in AD rats were all reduced. However, recent research showed that BACE1 inhibition has detrimental effects on cognitive and synaptic function [17]. In wild-type animals inhibiting BACE1 has the potential to lower endogenous Ab synthesis to the point where its neurotrophic and synaptotrophic capabilities are eliminated [18]. Evidence that Aβ has impairment of the function effects and has a good

impact on the processes underlying consciousness at low or physiological levels in addition to the documented neurotoxic effects induced by Ab.

Preventing gamma-secretase activity

Transmembrane-spanning protein molecules that contain more than a hundred, Notch, and N-cadherin, including APP, are cleaved by the membrane protease known as c-Secretase. The enzymatic part of presenilin is the presenilin subunit; polymorphisms in the presenilin Early-onset familial AD (FAD) are mostly genetic in origin8 due to the increased synthesis of the highly amyloidogenic Aβ 42variant. Promising treatment candidates for AD are thought to be drugs that target c-secretase. Other pathway obstructions are, most notably Notch signalling mechanism, which can result in severe adverse consequences when c-secretase is inhibited.

Increasing the enzymes that break down amyloid.

ECE, IDE, and ECE:

Insulin-degrading enzyme (IDE) Neprilysin (NEP), and endothelin conversion enzyme (ECE), are three proteases that have been demonstrated to cleave Evaluation of Aβ25 AAV5-ECE-1 injection in PS1/APP transgenic mice. Ab and plaques might diminish in the antecedent brain and hippocampal because regions close to the injection sites had significant production.

Another research contrasted the enhanced IDE and NEP expressions brought on by AAV. The IDE-n and NEP-n native forms as well as the IDE-s and NEP-s designed secreted versions were both expressed using AAV vectors[19]. In six-week research, total plaques and Ab were reduced into the hippocampus and cortex of mice given the NEP-n and NEP-s but not the IDE-n or IDE-s[20]. NEP may therefore be a suitable candidate for Alzheimer's Disease genetical therapy, yet not IDE.

Delivering antibodies against amyloid:-

To encourage its removal, polyclonal immunoglobulins or monoclonal antibodies that target Aβ has been utilized. Results from the research on animals have demonstrated that antibodies against Aβ can stop the production of oligomers, lower the amyloid burden in the brain, and enhance cognitive abilities. Many kinds of studies are now being conducted to assess the acceptability and effectiveness of these techniques in human patients.

anti-Ab single-chain AAV-encoding antibodies (scFv) were injected into the cortico hippocampal areas of AD mice models as part of a genetic therapy approach. In the neurons of the hippocampus, scFv expression was seen one year after injection. At the time of injection locations, amyloid deposits were significantly reduced, but there was no evidence of neurotoxic.

Increasing physiological APP pathway

Two opposing pathways—the amyloidogenic and the nonamyloidogenic pathways—can be used to digest APP by proteolysis[21]. The final one not only facilitates the release of the soluble APPsa but also stops the development of hazardous amyloid forms[22]. Many of the crucial physiological actions that APP performs are assumed to be mediated by the production of APPsa. When administered to mice in vivo, APPsa improves memory function and long-term potential (LTP) and exhibits critical physiological characteristics for synaptic plasticity and hippocampus function. APPsa knock-in fully restored spatial cognition in APP-KO mice.

INCREASE NEUROPROTECTION

Nerve growth factor

In some correlated animal studies of AD, growth factors of the nervous system prevent neuronal death[23]. The cholinergic neurons in the basal forebrain that experience quick and significant degeneration in AD are specifically stimulated and prevented from dying off by nerve growth factor (NGF)[24].

An initial and significant factor in cognitive and cell loss deterioration in AD is cholinergic neuron degeneration[25]. NGF levels do decrease in AD in the basal forebrain area[26]. Previous research using animal models of Alzheimer's disease has demonstrated that NGF may activate the cholinergic neurons, which were essential to maintain the cognitive functions and senescent in early Alzheimer's disease and stop their demise[27]. A 40-tailored delivery

approach is required to manage the localization and dissemination of growth hormones in the brain since they can have unintended negative consequences.

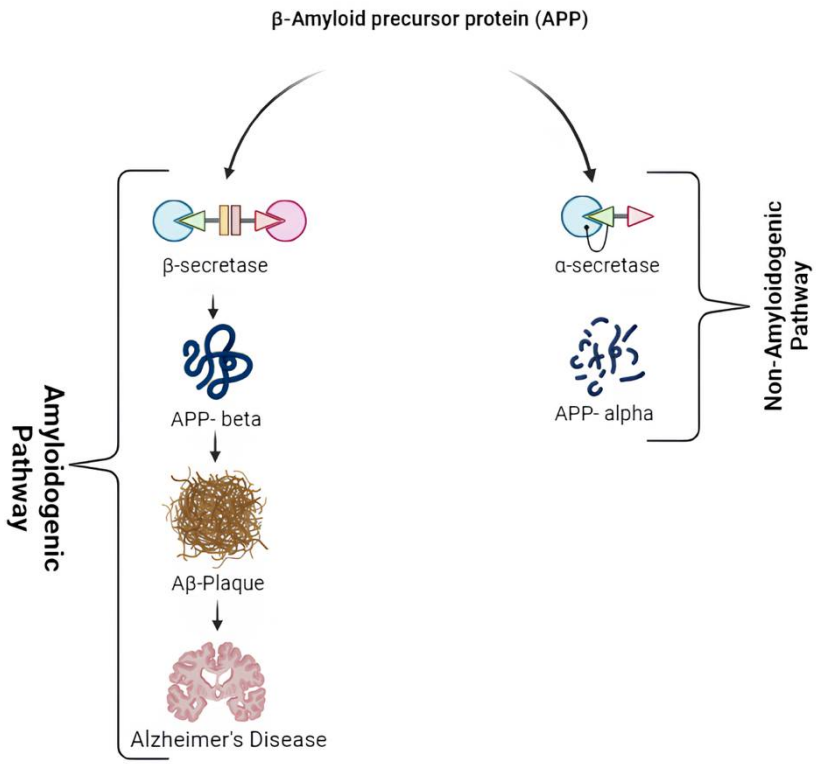

Fig. 2: **Amyloid Precursor Protein involved in Alzheimer's Disease.**
The major Pathway of Alzheimer's Disease involved in the APP is the formation of Aβ plaques.

Neurotrophic function of NGF.

The Neurotrophic family also contains NT-3, BDNF and NT-4/5. NGF was the first NT to be discovered and has been well investigated. Early research indicated that NGF, which is released by target cells to promote an equal generation of sensory and sympathetic neurons, is crucial for periphery neurological growth. Throughout development and adult neurogenesis, when the brain continuously produces new neurons by dividing neural stem cells, NGF is generated in the sea horse and cerebral cortex. Although hippocampus neurogenesis's biological function is unknown, it may play a role in learning and memory processes[20]. The cholinergic neurons, which are the main innervators of the cerebral cortex and hippocampus, are stimulated to grow and continue to function by NGF, which is produced by the area of the hippocampus and then transported across it to the terminals of the axons of the basal brain cortical neurons (BFCN). NGF is synthesized from two separate splice forms of mRNA resulting in the production of a long and a short precursor protein, which is subsequently processed into the trans-Golgi network. The mature form of NGF is subsequently created by the removal of the signal peptide by the enzyme furin, a signal peptide peptidase. NGF and the other NTs activate a variety of signalling routes in cells, including those that Ras involves, cAMP response elements binding protein and extracellular signal-regulated kinases (ERKs), via p75 receptors and binding to tropomyosin-related kinase A (TrkA) present into the BFCN. Along with its roles in brain development and cell treatment, Nerve growth factor influences synaptic functioning. Pro Nerve growth factor, which is more prevalent than Nerve growth factor, is also thought to have a role in apoptotic cell signalling via interacting with the p75 receptor. Surprisingly, no BFCN abnormalities were found despite the major effects on sympathetic ganglions and caused by gene deletion of NGF in mice. On the other hand, NGF injections helped cure cerebral atrophy of Down syndrome in a mouse model that showed degradation of the BFCN and lack of retrograde transport, indicating a neuroprotective role for NGF.

Neurotrophic factor from the brain.

The neurotrophin brain-derived neurotrophic factor (BDNF) appears in the entorhinal cortex and the hippocampus, two cortical regions. BDNF levels fall in Alzheimer's disease [28]. Management of neurotrophin brain-derived neurotrophic factor (BDNF) by a lentiviral vector to the entorhinal cortex enhanced learning and memory raised the level of the Synaptophysin is a protein and reduced the loss of neurons with early-life BDNF administration in an AD animal model (APP transgene mouse line J20). Five months after the BDNF chromosome mediated by lentivirus was inserted into the cerebral cortices of

mice, the animals were assessed. BDNF showed signs of neuroprotection. It's interesting to note that a reduction in plaque levels did not go along with this positive impact.
The homodimeric, relatively tiny (14kD) BDNF protein, considered a member of the NT family, has undergone little change throughout evolution. It is well known that the growth, survival, and development of nerve cells in both the peripheral nervous system and central nervous system (CNS) of the brain are aided by BDNF, which shares 50% of its amino acid sequence with NGF [29]. BDNF is highly expressed in the cerebral cortex and hippocampus, two regions of the brain crucial for mental and cognitive functions. In addition to being expressed by brain cells, BDNF is also found in muscles and endothelial cells, where it is thought to assist peripheral nerve cells. The BDNF gene has six distinct transcripts, and numerous promoters guarantee specific tissue expression. The primary locations of BDNF in a cell are the soma and dendrites, where it is delivered via secretory and post-Golgi vesicles. There is evidence of local translation since dendrites contain BDNF mRNA, the two distinct splice variants of mRNA that make up the TrkB receptor are translated. Although one of them is a complete form with kinase activity, the other is a condensed and kinase-activity-deficient variant with limited affinity for the p75 receptor. TrkB receptor binds BDNF with high affinity. It's interesting to note that a sizable quantity of BDNF is present in platelets in the blood, where it could act as a BDNF store to nourish neurons in the peripheral cortex. The involvement of BDNF in the plasticity of synapses is significant.
It is currently unknown if the reduced expression inside the brain is a cause of Alzheimer's illness or a result of the illness, but the act of BDNF in AD pathogenesis seems plausible [30]. However, BDNF supplementation in Alzheimer's disease may be a potential therapeutic strategy With the Blood-brainbarrier (BBB) in mind, The neurotrophin brain-derived neurotrophic factor (BDNF) should be administered intracranially, and a genetic therapy strategy would be suitable [31]. In a preliminary investigation, Tuszynski and colleagues described the outcomes of BDNF gene delivery in various animal models of AD. They discovered that BDNF treatment had a neuroprotective impact on cells located in the region known as the entorhinal cortex, which is a key afflicted area in AD and supplies the main input to the hippocampus, without changing the Aβ burden. Similar to this, BDNF treatment enhanced spatial learning behavior and elevated ERK phosphorylation, a marker of increased cell signalling, in elderly rats with middle entorhinal cortex abnormal expression of genes and cognition loss. Finally, for almost 40% of the genes that showed inconsistent expression levels, at least 30% of the normal gene expression was recovered.
The Swedish and Indiana mutation-containing APP is expressed by the APP transgenic mouse J20. These variants disrupt BACE1 and l'-secretase cleavage, respectively, which results in a rise in overall Aβ levels and the Aβ 42/Aβ 40 ratios. Additionally, they contribute to cognitive decline starting at 6 months old and maturity-dependent Aβ buildup starting at 3 months old. The water maze created by Morris and anxiety conditioning tests were used to measure the mice's performance on learning and memory tasks. When BDNF was administered to utilizing a lentiviral vector, to J20 mice and both ways injected into their cerebral cortex at the age of six months, it substantially enhanced the mice's performance without having any negative effects on the Aβ-load. The hippocampus areas CA1-3 received BDNF from the injection location, which is a fascinating development. According to genetic profiling, entorhinal cortex and hippocampal abnormal gene expression were partially corrected by BDNF administration. Finally, lentiviral production of BDNF enhanced visuospatial learning in elderly monkeys by preventing neuronal death of cells in an entorhinal cortex model of a primate with lesions of the effective pathway. When seen collectively, the BDNF gene delivery research yields encouraging findings, and once more in vivo investigations are finished, clinical trials are expected to be started.

NEUROTROPHIC FACTOR DERIVED FROM GLIAL CELLS

Glial cell-derived neurotrophic factor (GDNF) is a potent brain-derived factor with potential for therapy against a number of neurological disorders, involving Alzheimer's disease. In vivo, overexpression of the GDNF gene was achieved in hippocampus astrocytes of 3xTg-AD mice using lentiviral vectors. Six months later of GDNF overexpression, the memory and learning ability of 10-month-old 3xTg-AD mice were still present. GDNF treatment increased the expression of BDNF and caused neuroprotecting, but it failed to significantly diminish tau and amyloid pathology.

IGF1 and IGF2

In mice and rats, a growth factor similar to insulin 2 (IGF2) is essential for the consolidation of memory, and in people with Alzheimer's disease hippocampus, IGF2 expression is reduced. The injection of AAV-IGF2 entering aged mice's hippocampus that is wild-type improves memory and encourages dendritic spine development. Injection of AAV-IGF1 or AAV-IGF2 in APP Tg2576 mice's hippocampi reverses behavioural impairments, encourages the development of dendritic spines, and improves synaptic

communication [32]. The injection of IGF2 but not the injection of IGF1 enables a considerable decrease in amyloid levels. The results obtained show that IGF2R/IGF2 participates in the extra-cellular Aβ breakdown pathway and imply that IGF2R may scavenge for Ab[33]. In a separate study, mice with a cholinergic system-specific form of the green fluorescent protein (APP.PS1/ CHGFP) as well as control litter mates were given intracerebroventricular injections of IGF2 at six months, and this resulted in a decrease in the number of amyloid-containing hippocampal plaques and an increase in the hippocampal protein ACh- synthesizing enzyme.

Nrf2's activation of the antioxidant pathway

The pathogenesis of AD is largely dependent on damage from oxidative stress. An innate defense mechanism against oxidative stress is triggered by the binding of the gene transcription factor nuclear factor E2-related factor 2 (NRF2) to the antioxidants response element (ARE) enhancer sequence. This results in the simultaneous release of several protective enzymes and scavengers.

Nine-month-old transgenic mice with AD (PS1/APP animals) were utilized to introduce NRF2 bilaterally into the hippocampus using a lentiviral vector. Elderly APP/PS1 mice had their spatial learning deficiencies reduced. NRF2 genetic transfer was linked to a decrease in astrocytic stimulation, but not a microglial activity and stimulation of NRF2 targeted chromosome heme oxygenase1 in hippocampal neurons within six months after injection.

STIMULATING PATHWAYS MEDIATED BY AUTOPHAGY

The primary cellular route for the breakdown of protein turnover and proteins with a long life, known as autophagy, has been linked to Alzheimer's disease. There is evidence that indicates that enhancing the amounts of proteins associated with autophagy may have therapeutic value. Lentiviral-mediated transcription of berlin-1 reduced intracellular and extracellular β-pleated Aβ deposits in the cerebral cortex and hippocampal of APP mutant mice. A new approach to treating Alzheimer's disease may include enhancing autophagy and regenerating beclin-1.

NEPRILYSIN

Neprilysin's Function in Alzheimer’s Disease

An elevated level of Aβ, specifically Aβ 42, is associated with the accumulation of Aβ and later production of plaques of amyloid within the brain[34]. In healthy brains, the accumulating happens as we age, whereas in AD brains it is more noticeable. The rate of Aβ synthesis from APP, the rate of Aβ transport over the BBB, and the rate of Aβ breakdown in the brain parenchyma are the three kinetic parameters that govern the brain's steady-state Aβ concentration. Therefore, even a little alteration in metabolic rates has the potential to impact Aβ concentration, cause Aβ to accumulate, and result in AD pathology. Because of this, the Aβ-producing enzymes have been the focus of much research, and BACE1 and l'-secretase inhibitors have been developed with great effort. The vast BACE1 active site has been a difficulty, but effective BACE1 inhibitors are now being produced. However, the availability of BACE1 substrates in addition to APP reduces the use of these inhibitors. It is difficult to create compounds that precisely block Aβ production without having negative consequences due to the large number of l'-secretase substrates. However, the discovery of the Aβ-reducing enzymes has expanded our understanding of Aβ inhalation and unlocked newly developed biological targets linked to Aβ's catabolic pathways.

TARGET CANDIDATES FOR GENE THERAPY

APOE

Concentrating on APOE, the most significant Alzheimer's gene. Throughout the central nerve system, APOE controls the metabolism of lipoproteins and is also involved in the distribution of cholesterol, neuroplasticity and inflammation, among other crucial functions. Aβ aggregation and clearance are impacted by APOE's binding to Aβ.

The hippocampus Aβ and amyloid load are significantly altered in the PDAPP animal model for AD following Lentiviral delivery directly into the brain expressing three prevalent APOE isoforms in humans. Whether mouse APOE was present or not, the expression of APOE e2 following direct intracranial infusion of APOE e2 expressing lentiviral vector dramatically reduced hippocampal Aβ burden into the PDAPP model of the mouse [35]. In contrast, hippocampus Aβ 42 levels and amyloid buildup rose when APOE e4 was expressed during the absence of mouse APOE.

Recently, an AAV vector encoding the multiple human APOE alleles was injected into the lateral ventricles of Alzheimer's disease mice to transmit the ependymal layer, targeting the cerebral cortex of APOE-transgenic amyloid plaque-bearing mice [36]. Both interstitial fluid (ISF) and cerebrospinal fluid (CSF) contained human APOE proteins. The amount of solubility oligomeric Ab in the ISF, the rate of Aβ fibrillization and deposition, and the degree of neurological injury within the plaque were all influenced

by certain APOE isoforms. In contrast to APOE e2, which had a somewhat protective impact, soluble Aβ levels rose, synaptic loss worsened, and there were more dystrophic neurites within each deposit in AD animals that receive APOE e4. These findings imply that treatment strategies that aim to lower APOE e4 or raise APOE e2 might be advantageous in AD. When astrocytes—the cells that naturally create APOE—overexpress APOE e2, a lesser number of plaques are seen.

INHIBITING OF Acyl-CoA by CHOLESTEROL ACYLTRANSFERASE ENZYME

ACAT, an enzyme responsible for catalysing the production of cholesteryl esters, also controls the equilibrium level of cellular cholesterol [37]. Using AAVs encoding synthetic microRNA (miRNA) sequences targeting Acat1, the efficacy of a targeted genetic shutdown of Acat1 in the brain of a mouse, administered 10 months from the initial appearance of the disease, was investigated. Analysis after a year revealed that the delivery of the vector was tolerated well and enabled the mental levels Aβ and the whole APP to drop to levels similar to the complete elimination of Acat1.

ECE

Another membrane-integrated enzyme called ECE, which comes in the two isoforms ECE2 and ECE1, is connected to the breakdown of Aβ. Peptides are thought to be large macromolecules which influence a variety of biological action, including the constriction of blood vessels, and ECE is involved in their degradation by proteolytic enzymes. An extracellular binding site of zinc activity is present in ECE. ECE is restricted to layer V neurons in the cerebral cortex and hippocampus in the brain. The gene perturbation of ECE2-/-or ECE1+/- in mice led to a 1.3-fold rise in the brain of Aβ levels. ECE may break down Aβ in vitro and in vivo. In late-onset AD, ECE2 levels significantly dropped in the inferior parietal lobe, according to microarray research. Through the use of Western blot analysis and RT-PCR to analyze 14 post-mortem temporal neocortical tissues from individuals with proven AD, it was shown that ECE2 mRNA levels had increased 3–9-fold while ECE2 protein levels had increased 2.5–fold. Even if the mechanism governing the regulation needs more research, exposure of SH-SY5Y cells from neuroblastoma to Aβ 42 caused a drop after four hours, ECE2 expression, which was followed by a sharp rise after 24 hours. This indicates that ECE2 is not primarily down-regulated in Alzheimer's disease accumulation, and additionally, that a regulatory increase might happen in response to elevated Aβ levels. Additionally, it was shown that six AD individuals had reduced ECE1 levels in their CSF. To determine if AD is related to changing brain ECE levels, investigations involving additional patients are required.

APP

The direct decrease in the expression of APP by the use of siRNA may be a potential method to decrease the production of Aβ[38]. Studies on mice both in vitro and in vivo have demonstrated that APP may be knocked down using siRNA to lower levels of Aβ[39]. The quantity of APP mRNA effectively decreased the delivery of shRNA through HSV in a mouse model that has APP produced using a lentiviral vector and is targeted against APP [40]. The expression of shRNA decreased the levels of Aβ 40 more than 50%. However, suggests that APP or proteolytic fragmented thereof has significant physiological activities that would be impacted by APP downregulation. Such as although alive, APP-knockout mice have several undesirable characteristics, such as decreased weight and locomotor activity. Additionally, the siRNA-mediated decrease in APP in aged mice affects the brief-term and geographical working memory test, the Y-maze test, and immediate and geographical working memory in general. Therefore, it is important to carefully consider a form of gene therapy that uses siRNA to target APP.

CONCLUSION

The accumulation of Aβ usually occurs as a result of an imbalance between the formation of Aβ and elimination in AD patients. Therefore, a genetic treatment utilizing Aβ degrading enzymes might be an option in place of the foregoing methods. Recently, a variety of disorders have been effectively treated using gene therapy. Particular benefits include more security and the expression of gene selectivity offered by the creation of novel viral vectors. Numerous viral vectors employed now have little carcinogenic risk, in particular. Additionally, employing gene therapy rather than small chemical therapies may make it easier to up-regulate an enzyme.

Initial trials which clinically utilise ex vivo gene delivery have been completed, ameliorating AD pathogenesis. Genetic therapeutic has been widely explored in numerous Alzheimer's disease animal models with encouraging outcomes. Clinical studies employing in vivo techniques are probably going to be preferred in the future due to the time-consuming processes required for ex vivo gene transfer. Beyond safety, other crucial factors in the use of gene therapy include the right gene dose and effective targeting of the expression of genes. With a further in-depth understanding of the viral vectors, We

should be able to refine these vectors much further to offer incredibly specific to the site expression at different levels. Further consideration should be given to vector methods with switchable supporters, like the tetracycline system. Research on Alzheimer's disease on therapies based on disease-modifying medicines has very far only shown modest results in terms of treating symptoms. Several possible pathways in animal models of Alzheimer's disease have been evaluated with the help of the transfer of gene technologies that target certain brain areas; some of these pathways might merit consideration as prospective candidates for therapeutic applications in AD.

Similar to the majority of medical situations, developing novel therapies that modify the disease is highly dependent on several crucial factors, including a thorough understanding of the disease's natural course, its biological endpoints, clinical, and radiological, Selection of the patient group (LOAD, EOAD, hereditary history), formulation of meaningful outcome predictions based on illness evolution, and identification of biological markers that signal the efficacy (mechanism of action) of the medication. This is essential for novel, inventive biomedical treatments when only a small number of participants will be enrolled in phase I and phase II studies. Given that it is created to concentrate on a particular target and is administered selectively to afflicted brain areas, genetic treatment has a place in the fight against Alzheimer's disease. Additionally, it has the potential to provide light on the positive impacts of altering brain-related neural networks, which will aid in understanding the physiopathology of the illness and assist in halting its progression.

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