Possible Therapeutic Treatments for Alzheimer's Disease

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Alzheimer's Disease has been the most prevalent cause of dementia. Alzheimer's Disease causes rapid and irreversible cognitive decline, a decrease in problem solving skills and language, difficulties thinking, and memory loss. At the moment, there is no cure for Alzheimer's Disease. However, many studies are tackling different aspects of Alzheimer's to develop potential therapeutic treatments. For example, targeting amyloid-β and tau tangles, the two main components of Alzheimer's Disease, with immunotherapy can provide a possible treatment. In addition, genes like APOE also play a large role in Alzheimer's Disease. Specifically, people with APOE4 are shown to have a larger genetic risk factor for developing Alzheimer's Disease. Targeting APOE, specifically APOE4, through various methods, can serve as a possible therapeutic treatment. Furthermore, gene editing studies have shown that it is possible to improve Alzheimer's pathology by genetically modifying the genetic mutations associated with Alzheimer's Disease through CRISPR systems and base editing. While there are many ongoing studies that focus on targeting the mechanics behind Alzheimer's Disease, there are also many lifestyle prevention therapies and diets, such as the Mediterranean Diet, that are being studied to see if there is a possible way to reduce the chance of developing Alzheimer's by simply changing the way one lives. While all of these treatments are still in the experimental phase, there is a possibility one or more of these treatments can delay, prevent, or cure the symptoms of Alzheimer's Disease.

Introduction

Alzheimer's disease is a cognitive disorder, characterized by the degeneration of cells in the brain[1]. Although the precise causes of Alzheimer's disease are unknown, there are many risk factors, such as age, genetics, vascular diseases, head injuries, infections, and environmental and lifestyle factors[1].

Affecting 44 million people worldwide, Alzheimer's disease is now the most common cause of dementia[2–6]. 95% of people are diagnosed with Late Onset Alzheimer's which is usually caused by environmental factors and genetic predisposition. Less than 5% of people are diagnosed with Early Onset Alzheimer's, which is caused by genetic mutations on the amyloid precursor protein (APP) gene, presenilin 1 (PSEN-1) gene, or presenilin 2 (PSEN-2) gene[2,5,7]. Furthermore, one genetic factor that can heavily influence the development of Alzheimer's Disease is APOE, specifically APOE4. APOE4 plays a prominent role in increasing plaques and neurofibrillary tangles. However, researchers are testing APOE antisense oligonucleotides (ASO), which particularly bind to APOE mRNA to lower APOE gene expression. While this lowers overall APOE gene expression, there was 50 percent reduction of APOE4 levels, which will as a result lower tau, amyloid-β plaques, potentially delaying neurodegeneration[8]. Alzheimer's disease causes neurons to degenerate, which results in memory loss, a decline in thinking, loss of independence in day-to-day activities, and a complete change in personality[9].

The main hallmarks of Alzheimer's are the deposition and accumulation of amyloid-β and neurofibrillary tangles that are made up of hyperphosphorylated tau proteins[10,11]. On a molecular level, Alzheimer's can be classified by the buildup of amyloid-β plaques and neurofibrillary tau tangles. Amyloid-β plaques begin with altered cleavage of amyloid precursor protein by β-secretases and γ-secretases to produce insoluble amyloid-β fibrils. Amyloid-β then oligomerizes, which then diffuses into synaptic clefts, interfering with signaling of the synapses. Because of this, it forms into insoluble amyloid fibrils that become plaques[12]. Amyloid-β monomers can undergo modifications that increase their propensity to accumulate and form amyloid plaques that can spread throughout the brain[1]. Amyloid-β plays a large role in neural function and neurotoxicity, so more accumulation and denser plaques in hippocampus and amygdala can lead to damage of dendrites and axons, loss of synapses, and many cognitive impairments[1,7]. In addition to amyloid-β plaques, neurofibrillary tau tangles are also part of the molecular pathology of Alzheimer's disease. In normal circumstances, tau helps with intracellular trafficking and looks to provide microtubules with stability[13]. However, in Alzheimer's disease, hyperphosphorylated tau proteins can coil around each other making paired helical filaments, which can then accumulate in axons, dendrites, and the neural perikaryal cytoplasm, resulting in less cytoskeletal microtubules and tubulin-associated proteins[1]. The more hyperphosphorylated tau that accumulates, the more the amount of functional tau decreases, which can be

detrimental to axonal transport, leading to neurodegeneration (1st new one)

A combination of these cellular and molecular changes contribute to the progressive and irreversible cognitive decline observed in Alzheimer's disease. Symptoms include a decrease in problem solving skills, language, difficulties thinking, and memory loss[5,11]. Currently there are many studies of new therapeutic treatments that could delay or even prevent symptoms of Alzheimer's. Researchers focus on a specific aspect that is associated with the disease and design a treatment that can potentially make a significant change in people with Alzheimer's disease. In this review, I will explore the various developing therapeutic treatments that will possibly delay, prevent, or cure Alzheimer's Disease.

Tau and Amyloid Beta Immunotherapies

Large components of Alzheimer's disease are the buildup of amyloid-β in amyloid plaques[1,5] as well as neurofibrillary tangles that are made up of tau proteins[1,5,10]. With this, studies look to create a treatment that targets it to improve or prevent symptoms of Alzheimer's. Starting with the deposition of amyloid-β, the common hypothesis, also known as the amyloid cascade hypothesis, explores the idea that the "accumulation of amyloid-β as neurotic plaques, diffuse plaques, or oligomeric forms in the brain" is the main pathogenic event that causes Alzheimer's disease[1,5,14,15]. Amyloid-β immunotherapy could potentially be a good way of targeting the main pathogenic event that causes Alzheimer's[14,16]. Amyloid-beta immunotherapy consists of introducing the diseased brain to anti-amyloid β antibodies either with active (injection of an Aβ-containing immunogen) or passive (delivering of a recombinant monoclonal antibody) immunization[14,16]. This will allow the body's defense mechanisms to clear the amyloid-β similarly to how it would with other invasive pathogens[16]. The results showed that the amyloid plaques cleared, neuroinflammation decreased, neurotic dystrophy decreased, and the synapses were preserved with[16]. There is still uncertainty whether this therapeutic treatment will be effective in human patients with AD, but by testing the treatment on mouse models is a crucial step toward a potential treatment for patients with Alzheimer's.

Along with amyloid-β immunotherapies, there are also therapies that are attempting to target the other main component of Alzheimer's disease: neurofibrillary tangles composed of tau proteins[1,13,17]. In normal bodies, tau proteins allow for microtubule stability and help regulate intracellular trafficking[13]. Even before forming into tangles, tau goes through a series of modifications which include "hyperphosphorylation, acetylation- N- glycosylation, truncation"[1,13]. Like amyloid-β immunotherapies, there are also tau immunotherapies that present promising results for the future of Alzheimer's therapeutic treatments. The first successful active and passive immunization against tau used the PHF1 antibody, which targets tau peptides with phospho-epitopes like pSer396/404[13,17]. By using these agents on mouse models, tau levels and the behavioral phenotypes associated with tau were reduced[13,18]. Immunotherapies targeting various forms of tau, such as full length normal or mutant tau, or aggregated tau with active immunization have been shown to reduce tau pathology, with only a few reported harmful effects[13,18]. Active immunization is a promising option since it produces a long-lasting immune response, however, there is always a risk of unfavorable immune responses or detrimental effects on the normal protein[13,19]. Using a stronger adjuvant with the immunogen, such as the T-helper 1-inducing adjuvant, causes toxicity in the mice, but when using a more mild adjuvant, there are less adverse reactions[13,20]. To get better results with fewer adverse reactions, it is best if mild adjuvants are used with the tau immunogen[13]. Some of the other tau antibodies that have been tested are AADvac1 and ACI-35, which produced improved behavior of and reduced tau[13,21]. On the contrary, passive tau immunizations offer a safer alternative to the active immunization strategies. In addition to safer strategies, passive immunization can be more specific for the epitope that is being targeted. Because as the disease progresses and the epitope profile becomes modified, once the therapy is fully developed, the treatment can be fully designed to treat Alzheimer's at any given stage[13]. Some of the antibodies being tested with passive immunization are C2N-8E12 and BMS-986168, both of which show significant reduction in tau levels and provide a promising treatment for Alzheimer's disease. Furthermore, antibodies are being developed to slow down the progression of the disease by blocking the spread of tau pathology[13,22,23]. There are many antibodies that reduce tau and prevent further spreading without entering the neurons[13,19,22,23]. Although these antibodies will help with tau regulation, because most of the pathological protein is located inside the cell, the antibodies that will be the most effective in reducing tau are the antibodies that can target tau inside the cell[13]. Other possibilities of reducing tau tangles can be through vaccines that target hyperphosphorylated tau to reduce the chances of getting Alzheimer's disease[24]. Reducing tau tangles, a major component of Alzheimer's, with immunotherapies can be a way to effectively treat Alzheimer's. Amyloid-β and tau immunotherapies provide potential treatment options for Alzheimer's disease to prevent/delay symptoms of Alzheimer's disease.

Targeting APOE as a Possible Therapy for AD

Studies on Alzheimer's have found a correlation between the APOE (apolipoprotein E) gene and Alzheimer's Disease prevalence[10,11,15,25,26]. With this, there are possible therapeutic treatments for Alzheimer's that will target APOE in

order to delay the development or cure Alzheimer's disease. Produced primarily in the liver and brain, APOE plays a crucial role in neurobiology, lipid metabolism and neurodegenerative diseases[26]. There are 3 polymorphic forms of APOE including APOE2, APOE3, and APOE4[10,11,26]. Out of the three forms, it is believed that carriers of APOE4 have a higher chance of developing Alzheimer's Disease because APOE4 may cause some of the aspects that are associated with Alzheimer's disease[1,10,11,26]. APOE4 is thought to have toxic effects while APOE2 is thought to be more protective against Alzheimer's disease[10,11,26,27]. By seeing what aspects of Alzheimer's APOE4 effects, therapies will be able to target those aspects as well as APOE4 itself to potentially create a therapeutic treatment for Alzheimer's.

Amyloid- beta plaques are far more abundant in carriers of APOE4 with Alzheimer's disease that carriers of APOE3 or APOE2[10,11,27]. Studies have shown that APOE4 affects the formation of amyloid-β plaques by affecting the activity of gamma-secretase and impairs the lysosomal degradation of the plaques, thus affecting the clearing of the plaques[10]. APOE4 has also been shown to promote amyloid aggregation[10,11]. Like amyloid-β plaques, hyperphosphorylated tau may also be affected by APOE4[10,11]. It is suggested that because of their unique structure, APOE4 in neurons can escape the secretory pathway and directly contact tau proteins and promote its accumulation and hyperphosphorylation[10,11]. This means that APOE4 might be affecting two of the most important aspects that are associated with Alzheimer's Disease, meaning that if APOE4 is targeted for a therapeutic treatment of Alzheimer's Disease, it could be a possible effective treatment to delay symptoms of or cure Alzheimer's Disease in carriers of APOE4.

One possible treatment that targets APOE is APOE-directed anti-amyloid treatment[10]. Some in vivo experiments in mice show that utilizing antibodies that recognize human APOE3 and APOE4 and bind more to non-lipidated APOE can reduce amyloid-β deposition[10]. Amyloid-β plaques were also reduced using APOE antisense oligonucleotides[8,10]. APOE antisense oligonucleotides (ASO) bind to APOE mRNA to lower APOE gene expression. APOE4 levels have shown to decrease, which could also provide a way to reduce tau tangles and amyloid-β plaques[8]. While this lowers overall APOE gene expression, there was 50 percent reduction of APOE4 levels, which will as a result lower tau, amyloid-β plaques, potentially delaying neurodegeneration[8].However, these experiments were performed on mice and the relationship between APOE4 and amyloid-β is not fully understood. So, the full effect of this treatment still needs to be further researched but shows a promising future of becoming a potential treatment for Alzheimer's Disease[10].

Anti-APOE4 immunotherapy may also be used to target APOE4 to potentially cure Alzheimer's disease. Under stressful conditions, there is an increased production of intraneuronal APOE4 fragments[10]. Specifically, researchers have tested passive immunization with the HJ6.3 APOE monoclonal antibody to counteract the effects of APOE4[26]. Results showed that 60-80 percent of amyloid-β plaques were reduced in the cortex and hippocampus, the formation of new plaques were prevented, and brain function increased[26]. In addition to the HJ6.3 APOE monoclonal antibody, anti-APOE4 9D11, an antibody that is specifically targeted to the APOE4 isoform, was tested. In test subjects, this antibody inhibited the accumulation of amyloid-beta plaques, and formed APOE complexes that seemed to reverse cognitive impairment compared to the control mice[26]. Both of these antibodies reduced amyloid-β plaques, which in turn improved cognitive abilities[26]. Although these tests were done on mice, the results show a promising method that could improve and even reverse cognitive impairment in people with Alzheimer's Disease.

As mentioned before in this section, APOE4 is thought to have a toxic effect and is a risk factor for Alzheimer's Disease for anyone who carries APOE4. On the other hand, APOE2 is thought to be protective against neurodegeneration[10,11,26]. New studies suggest that injecting a viral vector that contains APOE2 can offset the effects of APOE4. Because this has been tested on mice and is a relatively new idea, the possibility of this therapy working has not been fully determined, but with further research, this idea could possibly cure Alzheimer's Disease.

APOE, specifically APOE4, has been shown to increase the chances of a person developing Alzheimer's Disease because it impacts many of the aspects that cause Alzheimer's Disease. APOE4 targeting therapies can potentially be a promising way to effectively reduce the risks of developing Alzheimer's Disease or possibly even cure Alzheimer's Disease in the future.

Gene Editing Therapies

Gene editing is a new and advanced technique that is being tested to help cure diseases and disorders by directly affecting the DNA and the genes that are mutated by the disease. Gene editing is being researched for many diseases including Alzheimer's Disease. Base editing and nuclease-based genome editing show a promising future of creating an effective therapeutic treatment for Alzheimer's Disease.

The CRISPR/Cas9 genome editing method has been used widely for a decent amount of time. CRISPR systems target a target DNA sequence through base pairing with a guide RNA[28]. CRISPR systems have 2 main components: a Cas9 enzyme and a single-guide RNA[28,29]. Although CRISPR can cause DNA breaks, the methods of CRISPR are being reviewed and advancing to provide effective gene editing without indels[28–31]. Such advancements include improving the DNA specificity of CRISPR-based agents and expanding the

scope of CRISPR/Cas enzymes[31]. With the help of these advancements, CRISPR methods could effectively delay symptoms or prevent Alzheimer's Disease.

CRISPR-Cas9 has been used to correct a pathogenic APP(Swe) mutation in primary AD patient cells with high precision and specificity. In addition to this, BACE1 has been shown to be crucial to the production of amyloid- peptides[29,32]. By loading the Cas9 enzyme and the single-guide RNA targeting BACE1 into an amphiphilic nanocomplex which allowed for efficient gene targeting in post-mitotic neurons in vivo, amyloid-β pathologies as well as cognitive defects were both reduced[32]. Targeting BACE1 is another way CRISPR could help treat Alzheimer's Disease. Furthermore, as mentioned previously in the paper, carriers of the APOE4 allele have a genetic risk for Alzheimer's Disease since the APOE4 gene affects the main components associated with Alzheimer's. CRISPR genome editing can possibly target APOE4 and genetically convert it to APOE3 OR APOE2[10]. Although this method has not been fully researched or tested, it could provide a way to target a large genetic risk factor associated with Alzheimer's Disease.

In addition to nuclease-based CRISPR gene editing methods, base editing can also be used to treat many diseases such as Alzheimer's Disease. Base editing is the process of precisely changing the target base pair into a new base pair in the living cell by using a deaminase without causing double-stranded DNA breaks[30,33–36]. Base editing converts C-G pairs to T-A pairs and converts A-T pairs to G-C pairs without any causing DNA breaks[33,34,36]. The initial base editor utilized a cytidine deaminase and catalytically impaired Cas9 protein from converting C-G base pairs to T-A base pairs at sites of interest[33,36–39]. The newly developed base editors are beneficial for direct installations and corrections of the point mutations in the body[31]. Further versions of base editing have been developed since the initial CBE, such as ABE's (adenine base editors). Adenine base editors can convert A-T base pairs to G-C base pairs without DNA breaks[32,35]. This base editing strategy was able to provide a treatment for Hutchinson–Gilford progeria syndrome (HGPS) in mice[32]. Hutchinson-Gilford progeria syndrome is caused by a dominant-negative C•G-to-T•A mutation in LMNA[32]. This means that this adenine base editor has the potential to correct the mutation that causes HGPS. When tested with a lentiviral delivery to cultured fibroblasts from children with HGPS, there was 87-91% correction of the pathogenic allele, reduced levels of progerin, and correction of nuclear abnormalities[32]. If the base editing strategy can be used to cure Hutchinson-Gilford Progeria Syndrome, then base editing could be a promising way to help patients with Alzheimer's by correcting the mutations that cause Alzheimer's Disease.

Even though only a small portion of patients have Alzheimer's Disease that is caused by a gene mutation in APP, PSEN1, or PSEN2, a base editing method that targets the mutation in the APP gene could be a potential treatment for Alzheimer's Disease[40,41]. Furthermore, the cleavage of the APP protein by a beta secretase can cause formation of amyloid-beta plaques, which are a major component of Alzheimer's Disease[41]. The A673T mutation is shown to reduce the cleavage of β-secretase by 40%, so in theory, if this mutation is inserted into the APP protein by means of base editors, it could reduce the amyloid- plaques[41]. When the A673T mutation was introduced into the APP protein in modified HEK293T cells, 53% of the cells showed reduction of amyloid-beta plaques[31]. With more research, base editing could be a promising treatment that could be used to treat Alzheimer's Disease.

Gene editing is the path towards the future of therapeutic treatments for Alzheimer's Disease and many other diseases. By identifying and locating the many genetic mutations that occur and are involved in Alzheimer's Disease, it is possible for nuclease-based Cas9 genome editing methods and base editing to provide a potential treatment for Alzheimer's Disease.

Lifestyle Prevention Therapies

Along with therapies that target aspects of Alzheimer's Disease within the body, many lifestyle choices have been shown to prevent or delay symptoms of Alzheimer's. Incorporating physical activity, change in diet, cognitive challenges, and socialization into one's daily life can potentially lower the risk of one getting Alzheimer's disease[5].

For elderly individuals, physically active means either doing moderate intensity exercise for 30 minutes at least five days a week or 20 minutes of vigorous intensity exercise for at least three days a week[42]. Research shows that moderate physical activity is associated with better cognitive function[5,9,42]. For example, physical activity helps amplify hippocampal neurogenesis in rodents[5]. In addition, research showed that compared to physically inactive middle-aged people, physically active middle-aged people showed a better response to cognitive assignments[42]. Even middle-aged people who transition to an active lifestyle have demonstrated significant improvements in cognitive function, although this may not always occur for people 60-80 years old[42]. This could be because exercise promotes the release of neurotrophic factors such as nerve growth factor and vascular endothelial growth factor, increasing neurogenesis and neural plasticity[5]. In addition, exercise can cause the reduction of free radicals in the hippocampus and increase superoxide dismutase and endothelial nitric oxide synthase[5]. With these promising results, it can be reasonably inferred that simply changing the amount of physical activity one gets can delay or help prevent

Alzheimer's Disease.

Various vitamins and diets have been shown to increase neuroprotection and potentially help maintain cognitive abilities[9]. Research has been done to see if vitamin B supplements provide neuroprotection for people. The study produced mixed results, making vitamin B an unreliable therapy to protect the brain from Alzheimer's[5]. However, vitamin D and E supplementation led to improvements in cognitive performance[5,43]. Furthermore, changes in diet can also offer a potential therapy against Alzheimer's Disease. For instance, there is a potential correlation between alcohol, specifically red wine consumption, and Alzheimer's disease prevention because of its composition of polyphenols[5,27]. One type of polyphenol that is found in red wine is Resveratol, which has been studied to see if there is a correlation between its consumption and reduced risk for Alzheimer's disease. Resveratol has been shown to be an anti-inflammatory, vasodilator, and even provides cardioprotection[5,6]. Resveratrol can activate SIRT1, which can allow for the protection of neurons from apoptosis and oxidative stress. In addition to this, the activation of SIRT1 induced by resveratrol reduced the activation of the NF-$\kappa\beta$ signaling pathway in glial cells exposed to Aβ[5,43]. Although additional research must be conducted to reach a conclusion, the composition of red wine can provide a basis for researchers to see if red wine consumption can reduce risks for Alzheimer's Disease.

Furthermore, diets such as the Mediterranean and Asiatic diets have shown to improve neuroprotection and could potentially be a lifestyle prevention therapy[5]. The Mediterranean Diet is based on low consumption of saturated fatty acids and high consumption of unsaturated fatty acids with many foods such as legumes, vegetables, olive oil, and polyphenols such as oleuropein aglycone[43]. These foods have been shown to interfere with and reduce amyloid aggregation, a significant component of Alzheimer's Disease[5,9]. The foods in the Mediterranean diet have been reported to have anti-inflammatory effects and lead to less cognitive decline[5,27,44]. As diets with low saturated fat consumption have been shown to be beneficial, we can infer that foods with a high level of saturated fatty acids will increase the chances of one developing Alzheimer's Disease[5,43]. In addition to the Mediterranean Diet, the Asiatic Diet is based on a large consumption of green tea, curcumin, and a supplement called Ginkgo Biloba[5]. These foods can protect against memory decline and also decrease amyloid beta aggregation. Although the potentially toxic effects of this diet aren't thoroughly researched, it can potentially be a way to prevent Alzheimer's Disease[5]. By simply changing a diet or consuming foods that are part of the Mediterranean and the Asiatic Diet, one can potentially prevent developing Alzheimer's Disease.

Furthermore, cognitive challenges and activities such as psychoeducation and computer courses stimulate the brain and can lead to an increase in neuronal density, which helps brain plasticity. Including cognitive challenges in everyday lives can help delay or prevent the development of Alzheimer's Disease[5]. Along with practicing cognitive challenges, it is also crucial for people to incorporate socialization into their daily lives[5]. Lack of socialization can result in loneliness, which has been shown to increase the chances of Alzheimer's Disease[5]. Many simple changes in one's lifestyle could decrease the chances of developing Alzheimer's disease. Changing the way one lives could be a simple and easy method to prevent Alzheimer's disease.

Conclusions

Alzheimer's Disease affects millions of lives worldwide. Alzheimer's disease prevalence is increasing, and there has yet to be a definite treatment that could prevent or delay disease symptoms. However, there are many possible therapeutic treatments, which target different components of Alzheimer's Disease. Through amyloid-β and tau therapies, APOE-targeting treatments, CRISPR and base editing strategies, and even simple lifestyle adjustments may be able to provide patients with a cure or help people prevent the development of Alzheimer's Disease. Once fully developed, these treatments will provide people with longer time to preserve and use their cognitive abilities, allowing people with Alzheimer's to lead a normal life longer than what it would have been possible without the treatment.

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